Pharmacokinetics and Metabolism of Natural Methylxanthines in Animal and Man

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Contents

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Abstract Caffeine, theophylline, theobromine, and paraxanthine administered to animals and humans distribute in all body fluids and cross all biological membranes. They do not accumulate in organs or tissues and are extensively metabolized by the liver, with less than 2% of caffeine administered excreted unchanged in human urine. Dose-independent and dose-dependent pharmacokinetics of caffeine and other dimethylxanthines may be observed and explained by saturation of metabolic pathways and impaired elimination due to the immaturity of hepatic enzyme and liver diseases. While gender and menstrual cycle have little effect on their elimination, decreased clearance is seen in women using oral contraceptives and during pregnancy. Obesity, physical exercise, diseases, and particularly smoking and the interactions of drugs affect their elimination owing to either stimulation or inhibition of CYP1A2. Their metabolic pathways exhibit important quantitative and qualitative differences in animal species and man. Chronic ingestion or restriction of caffeine intake in man has a small effect on their disposition, but dietary constituents, including broccoli and herbal tea, as well as alcohol were shown to modify their plasma pharmacokinetics. Using molar ratios of metabolites in plasma and/or urine, phenotyping of various enzyme activities, such as cytochrome monooxygenases, N-acetylation, 8-hydroxylation, and xanthine oxidase, has become a valuable tool to identify polymorphisms and to understand individual variations and potential associations with health risks in epidemiological surveys.

Keywords Absorption · Age · Alcohol · Bioavailability · Caffeine · Cytochromes · Diet · Diseases · Distribution · Drugs · Excretion · Gender · Hormones · Interactions · Metabolism · Obesity · Paraxanthine · Pharmacokinetics · Physical exercise · Smoking · Theobromine · Theophylline

Abbreviations

1,3,7DAU	6-Amino-5(*N*-formylmethylamino)-1,3-dimethyluracil
1,3,7TMU	1,3,7-Trimethyluric acid
1,3DMU	1,3-Dimethyluric acid
1,7DAU	6-Amino-5-(*N*-formylmethylamino)-3-methyluracil
1,7DMU	1,7-Dimethyluric acid
1MU	1-Methyluric acid
1MX	1-Methylxanthine
3,7DAU	6-Amino-5-(*N*-formylmethylamino)-1-methyluracil

3,7DMU	3,7-Dimethyluric acid
3MU	3-Methyluric acid
3MX	3-Methylxanthine
7MU	7-Methyluric acid
7MX	7-Methylxanthine
AAMU	5-Acetylamino-6-amino-3-methyluracil
AFMU	5-Acetylamino-6-formylamino-3-methyluracil
AUC	Area under the concentration versus time curve
C_{max}	Peak plasma concentration
CYP	Cytochrome P450
GSH	Glutathione
IBW	Ideal body weight
K_a	Absorption rate constant
K_e	Elimination rate constant
K_m	Michaelis–Menten constant
NAT2	*N*-Acetyltransferase 2
TBW	Total body weight
T_{max}	Time to reach the peak plasma concentration

1 Introduction

Caffeine metabolism and pharmacokinetics have been reported in several reviews and monographs (Arnaud and Welsch 1982; Arnaud 1984, 1987, 1988, 1993a, b, 1998; Anonymous 1991). Reviews on theophylline (Arnaud and Welsch 1982; Hendeles et al. 1986; Anonymous 1991) were published because of its wide application as an active component of a variety of over-the-counter pharmaceutical products and drugs. A few reviews have been published on theobromine (Tarka 1982; Anonymous 1991), but there is no review on paraxanthine, perhaps because it can be found in plants only in trace amounts and is identified in human urine (Salomon 1883). This chapter highlights some of the present knowledge, including the most recently published studies on these four methylxanthines.

2 Caffeine

2.1 Absorption

Absorption and bioavailability of caffeine were generally similar between humans, dogs, rabbits, rats, and mice (Walton et al. 2001). In animals and man, absorption is *characterized* by rapid and complete gastrointestinal absorption (Arnaud 1976;

Arnaud and Welsch 1980a; Yesair et al. 1984). In man, 99% of the administered dose was absorbed in 45 min (Blanchard and Sawers 1983a), mainly from the small intestine but also 20% from the stomach (Chvasta and Cooke 1971). The absolute bioavailability of caffeine (5 mg/kg) in healthy adult male volunteers showed a rapid oral absorption with the time to reach peak the peak plasma concentration (T_{max}) of 29.8 ± 8.1 min and a peak plasma concentration (C_{max}) of 10.0 ± 1.0 μg/mL. From comparison of the caffeine area under the concentration versus time curve (AUC) after intravenous and oral doses, a complete absolute bioavailability of caffeine was demonstrated (Blanchard and Sawers 1983a). Caffeine pharmacokinetics were independent of the route of administration as shown by superimposable plasma concentration curves, suggesting that there is no important hepatic first-pass effect. Caffeine absorption from food and beverages does not seem to be dependent on age, gender, genetics, and disease or consumption of drugs, alcohol, and nicotine. Caffeine absorption from cola and chocolate was delayed, with T_{max} of 1.5–2 h instead of 0.5 h for a capsule and the C_{max} values were 1.57 for cola, 1.50 for chocolate, and 2.05 μg/mL for the capsule (Mumford et al. 1996). Pharmacokinetics of caffeine (100 mg) and its dimethylxanthine metabolites studied after inhalation in heroin users and compared with intravenous and oral administration in healthy volunteers showed a rapid and effective absorption after inhalation with an approximate bioavailability of inhaled caffeine of 60% in experienced smokers (Zandvliet et al. 2005). The efficacy of percutaneous caffeine absorption has been demonstrated in premature infants treated for neonatal apnea (Morisot et al. 1990).

2.2 Distribution

Caffeine enters the intracellular tissue water and is found in all body fluids – plasma, cerebrospinal fluid, saliva, bile, semen, breast milk, and umbilical cord blood as well – as in all tissue organs. There is no long-term accumulation of caffeine or its metabolites in the body as seen by whole-animal autoradiography using radiolabeled caffeine (Arnaud 1976).

2.2.1 Tissues

The tissue distribution 1 h after intravenous injection of caffeine into rabbits showed that the caffeine tissue-to-blood concentration ratio was approximately 1.0 with concentrations of 3.32 ± 0.47 μg/g. Exceptions included fat (0.79 ± 0.21 μg/g), adrenals (1.96 ± 0.36 μg/g), liver (4.88 ± 0.48 μg/g), and bile (8.97 ± 0.701 μg/g), in which the ratios were 0.2, 0.6, 1.5, and 2.7, respectively (Beach et al. 1985). Microdialysis applied with simultaneous subcutaneous infusion of caffeine and theophylline (20 mg/kg) to measure their concentrations in blood, adipose tissue, muscle, and liver of rats showed that caffeine was found to be evenly distributed in an in vitro test (Ståhle et al. 1991). While there was no

difference between caffeine and theophylline for in vitro recovery, the in vivo recovery of theophylline was significantly less than the recovery of caffeine in brain, liver, muscle, and adipose tissue and this difference was significantly larger in the brain than in other tissues (Ståhle 1991).

There is no blood–brain barrier limiting the passage of caffeine through tissues. Therefore, from mother to fetus and to the embryo, an equilibrium can be continuously maintained. The disposition of caffeine and its metabolites, theophylline, theobromine, and paraxanthine, in the 20-day fetal and adult brains following a single maternal dose of 5 or 25 mg/kg caffeine showed that fetal and adult caffeine AUC values did not differ between the brain and plasma at either dose (Wilkinson and Pollard 1993). The brain-to-plasma ratio was close to 1 for a dose of 100 mg/kg and was lower for 10 mg/kg (0.6–0.7) and changed with time for 1 mg/kg, from 0.8 up to 1.9 after 4 h. When the dose of caffeine administered orally in the rat changed by 10 or 100 times, the AUC changed by 22 and 385 times in brain (Latini et al. 1978). Caffeine was found to be evenly distributed with a free concentration of approximately 120 μM and the rate of penetration into brain extracellular space was higher for caffeine than for theophylline (Ståhle et al. 1991). The pharmacokinetics of caffeine in the blood and cerebrospinal fluid were similar (Vickroy et al. 2008).

Similarly, caffeine is readily distributed to the fetus (Kimmel et al. 1984). The amniotic fluid to maternal plasma concentration ratio was higher for caffeine than for its major metabolite, paraxanthine, throughout gestation, and increased near term for both compounds. Both compounds distributed nearly homogeneously to fluids and tissues of the 29-day fetus, with mean fetal-to-maternal concentration ratios of 0.7 for paraxanthine and 0.9 for caffeine. The free fraction of caffeine was constant during gestation (about 0.8), while that of paraxanthine increased from 0.25 to 0.4 (Dorrbecker et al. 1988a). Caffeine is also readily excreted in milk (Gilbert et al. 1985), but there are significantly lower concentrations of caffeine and dimethylxanthine metabolites in milk when compared with serum in rabbits (McNamara et al. 1992), while in milk of lactating dairy cows the caffeine concentration was similar to the serum concentration 1.5–24 h after caffeine administration (DeGraves et al. 1995).

The situation in man is similar. After oral or intravenous doses of 5–8 mg/kg, mean plasma concentrations of 8–10 mg/L are observed. The caffeine plasma concentrations then decrease more rapidly than those of its metabolite paraxanthine, so in spite of important interindividual differences, paraxanthine concentrations become higher than those of caffeine within 8–10 h after administration. A good correlation was observed between the concentrations of caffeine in serum and in saliva, so noninvasive salivary measurements may be used for determination of caffeine pharmacokinetics in man (Scott et al. 1984). The caffeine concentrations in saliva were 65–85% of those in plasma (Callahan et al. 1982). After a 200 mg caffeine oral load in healthy adults, the saliva concentrations of caffeine, paraxanthine, and theophylline were lower than the plasma concentrations ($P < 0.001$), whereas the theobromine concentrations in plasma and saliva were similar. The saliva concentrations of these methylxanthines were higher than the free plasma concentrations ($P < 0.001$) (Rodopoulos and Norman 1996). The median AUC

value for caffeine measured from saliva was 72% of that from serum, with variations of 56–95% between individuals (Spigset et al. 1999a).

In newborn infants, similar levels of caffeine concentration were found in plasma and cerebrospinal fluid (Anonymous 1991). Caffeine and its metabolites were detected in cerebrospinal fluid of patients with severe traumatic brain injury and increased concentration was associated with significant favorable outcomes (Sachse et al. 2008).

Urinary and umbilical cord blood analyses of caffeine have been correlated with reported intake throughout pregnancy ($P < 0.0001$) (Grosso et al. 2008). Ex vivo perfusion of the human placenta showed that caffeine crossed the placenta by passive diffusion (Mose et al. 2008) and analyses of human fetal gonads found that the caffeine concentrations were the same as in plasma (Anonymous 1991; Arnaud 1993a).

Transcutaneous collection allowing quantitation of caffeine that diffuses directly through the skin from within the body in healthy volunteers taking caffeine orally showed that the amount of caffeine collected was linearly related to the plasma AUC. Increased sweating carried out on one arm of each subject maintained at 40°C to induce local sweating showed a larger contribution to transdermal collection (40%) in the first 5 h and much less (14%) after 10 h (Conner et al. 1991). Caffeine, paraxanthine, and theobromine measured from transdermal sweat patches that continuously collected and stored analytes lost through the skin showed caffeine and paraxanthine accumulated at comparable rates, while theobromine accumulated more slowly (Delahunty and Schoendorfer 1998).

Values of the milk-to-serum concentration ratio of 0.52 and 0.81 were found in breast milk. As the binding of caffeine to constituents of serum and whole breast milk was 25.1 and only 3.2%, respectively, it was suggested that all the binding in breast milk was accounted for by the butterfat content (Arnaud 1993a).

2.3 Excretion

In both animals and man, renal excretion dominates. The metabolic disposition of [1-Me-^{14}C]caffeine studied and compared in the rat, the mouse, and the Chinese hamster showed no interspecies differences in urinary excretion of radioactivity, with 67–70% of the administered dose recovered (Arnaud 1985) and after the administration of [8-^{14}C]caffeine to various mouse strains, 73–89% of the dose was recovered in urine (Arnaud et al. 1989). In rabbits, after the administration of [2-^{14}C]caffeine, 82% of the administered radioactivity was recovered in urine (Beach et al. 1985). After oral administration of [2-^{14}C]caffeine and [1-Me-^{14}C] caffeine in rats, fecal excretion amounted to 2–7% of the administered dose. Most of the fecal excretion corresponded to caffeine metabolites secreted from enterohepatic cycling with intestinal and biliary secretion (Arnaud 1976). With [1-Me-^{14}C]caffeine administered to rats, mice, and Chinese hamsters, no interspecies differences appeared in fecal excretion of caffeine metabolites and 3–6% of the

administered dose was recovered (Arnaud 1985). After the administration of [8-^{14}C]caffeine to various mouse strains, 7–12% of the dose was recovered in feces (Arnaud et al. 1989). After oral administration of radiolabeled caffeine in man, the 48-h fecal excretion amounted to 2–5% of the dose. The products identified in the feces of human volunteers were 1,7-dimethyluric acid (1,7DMU), 1-methyluric acid (1MU), 1,3-dimethyluric acid (1,3DMU), 1,3,7-trimethyluric acid (1,3,7TMU), and caffeine, which amounted to 44, 38, 14, 6, and 2% of fecal radioactivity, respectively (Callahan et al. 1982).

Caffeine and its dimethylxanthine primary metabolites are extensively reabsorbed in the renal tubule and their renal clearances were highly urine flow dependent, so urinary excretion varied with urine output. About 70% of the administered oral dose of caffeine (7.5 mg/kg) was recovered in urine (Tang-Liu et al. 1983) but less than 2% of caffeine was excreted unchanged in the urine. This low caffeine urine excretion (0.5–2%) is explained by a 98% renal tubular reabsorption. For higher caffeine intake (1 g, 10–12 cups of coffee), the recovery of caffeine in urine was from 0.74 to 0.91% of the dose and the urinary concentration was 14 mg/L. A good correlation was found between urinary and plasma caffeine concentrations (Birkett and Miners 1991).

2.4 Pharmacokinetics

Important pharmacokinetic differences have been reported between animal species, making the extrapolation between species difficult. In most studies performed in animal species, dose-independent pharmacokinetics for caffeine were reported and analyzed according to a one-compartment open model, while at higher doses applied in toxicology, dose-dependent pharmacokinetics were observed with lower plasma clearances. When the dose of caffeine administered orally to rats changed by 10 or 100 times, the AUC by changed by 45 and 746 times in plasma (Latini et al. 1978). These dose-dependent kinetics effects reported in animals can be explained by a saturation of metabolic transformation of caffeine (Bortolotti et al. 1985; Arnaud 1993a, b). Linear or nonlinear caffeine pharmacokinetics may be observed depending on the route and the rate of administration (Lau et al. 1995). The systemic clearance of total caffeine was 3.83 $\pm$ 1.94 and 1.14 $\pm$ 0.80 mL/min/kg and the unbound systemic clearance was 5.09 $\pm$ 2.60 and 1.41 $\pm$ 0.71 mL/min/kg in rabbit adults and the pups, respectively. A significant decreased caffeine clearance in the pups is thus demonstrated when compared with the adults (McNamara et al. 1992).

There is minimal (Yesair et al. 1984) or no first-pass metabolism for caffeine in human and the caffeine elimination is a first-order process in healthy human (Arnaud 1993a) and is described by a one-compartment open model system in the dose range of intake of 2–10 mg/kg observed in the population (Blanchard and Sawers 1983a; Newton et al. 1981; Bonati et al. 1982). Dose-dependent kinetics were observed when caffeine plasma levels were higher than 30 mg/L in the case

of acute intoxication in an infant (Jarboe et al. 1986), but in adult subjects some metabolic transformations can be saturated in lower dose range of 1–4 mg/kg, particularly demethylation into paraxanthine, which is selectively catalyzed by CYP1A2 (Tang-Liu et al. 1983; Cheng et al. 1990; Denaro et al. 1990; Arnaud and Enslen 1992). To explain why epidemiology studies reported a nonlinear dose response between coffee consumption and health risks, the presence of a dose-dependent metabolism of caffeine was studied. Under chronic dosing conditions, healthy subjects received a placebo, a low dose of caffeine (4.2 mg/kg/day caffeine), or a high dose of caffeine (12 mg/kg/day caffeine) in decaffeinated coffee and in six divided doses spaced throughout the day. Caffeine clearance fell from 0.118 L/h/kg (placebo treatment) to 0.069 L/h/kg (low dose; $P < 0.005$) and to 0.54 L/h/kg (high dose; $P < 0.001$). The formation and metabolite clearances of paraxanthine, the major primary metabolite of caffeine, also decreased when comparing the low and high doses ($P < 0.05$). These results suggest that caffeine metabolism is dose-dependent, resulting in nonlinear elimination (Denaro et al. 1990). When caffeine clearance was determined on separate occasions using a single oral caffeine (70-, 200-, and 300-mg) dose, caffeine exhibited dose-dependent pharmacokinetics, particularly in subjects who showed high initial clearance with the lowest dose of caffeine. This significant decrease in caffeine clearance with increasing dose from 70 to 300 mg ($P < 0.01$) indicated a saturable caffeine metabolism in the dose range tested (Cheng et al. 1990). In addition to the dose, the plasma kinetics of caffeine can be influenced by the presence of food in the stomach and gastric emptying (Brachtel and Richter 1988). Both genetic and environmental factors are suggested as an explanation for the larger variability of caffeine clearance (Nagel et al. 1990). Fluid intake may also modify renal clearance and thus affect caffeine pharmacokinetics (Trang et al. 1985). Chronovariation in caffeine elimination appears to be small (−25 to 16%) in most of subjects (Levy et al. 1984). Measurements of caffeine clearance, acetylation phenotype, and urinary molar ratios of metabolites [5-acetylamino-6-formylamino-3-methyluracil (AFMU) plus 1-methylxanthine (1MX) plus 1MU to1,7DMU] were not changed when caffeine was given orally at 10 a.m. and at 10 p.m. (Hashiguchi et al. 1992). Surprisingly, sleep deprivation in healthy subjects receiving 2.1, 4.3, or 8.6 mg/kg caffeine showed a significantly ($P < 0.05$) and disproportional increase in the dose-normalized caffeine AUC. Clearance and the paraxanthine-to-caffeine ratio were significantly decreased with increasing dose, suggesting that under severe sleep deprivation caffeine exhibited dose-dependent pharmacokinetics (Kamimori et al. 1995).

After a single dose of caffeine (4 mg/kg) peak plasma concentrations were observed at 1–2 h with half-lives of 2.5–5 h (Anonymous 1991; Arnaud 1993a). Larger variations of caffeine plasma half-lives from 2.3 to 9.9 h were reported, indicating substantial intersubject variability in its elimination (Blanchard and Sawers 1983a). The half-lives of theophylline and theobromine (6.2–7.2 h) were significantly longer than those of caffeine and paraxanthine (4.1–3.1 h) (Lelo et al. 1986a). A peak serum level of 13.5 ± 2.9 mg/L for caffeine occurred 1 h after the administration and was delayed 1 h later for theophylline when caffeine (10 mg/kg)

and theophylline (5 mg/kg) were given orally to asthmatic young patients. The half-life of caffeine was 3.9 ± 1.4 h and was shorter than the half-lives of theophylline with a twofold higher dosage level (Becker et al. 1984). After oral administration, the total plasma clearance of caffeine was similar to that of paraxanthine (2.07–2.20 mL/min/kg) and approximately twofold higher than the total plasma clearances of theophylline and theobromine (0.93–1.20 mL/min/kg). The unbound plasma clearances of caffeine and paraxanthine were also similar in magnitude (3.11–4.14 mL/min/kg) and also higher than those of theophylline and theobromine (1.61–1.39 mL/min/kg) (Lelo et al. 1986a). In nonsmoking subjects, the mean partial clearance of caffeine to paraxanthine was approximately eightfold and 23-fold greater than that to theobromine and theophylline, respectively, confirming earlier reports that paraxanthine is the major metabolite of caffeine in humans (Lelo et al. 1986b). At the steady state, the volume of distribution of theophylline (0.44 L/kg) was lower than that of the other methylxanthines (0.63–0.72 L/kg) and the unbound volumes of distribution of theophylline and theobromine (0.79 L/kg) were lower than the unbound volume of distribution of caffeine (1.06 L/kg), which was similar to that of paraxanthine (Lelo et al. 1986a).

2.5 Metabolism

To assess the validity of the interspecies toxicokinetics of caffeine, theobromine, theophylline, and paraxanthine, absorption, bioavailability, and the route of excretion were generally similar between humans and dogs, rabbits, rats, and mice but there were interspecies differences in the route of metabolism, and the enzymes involved in this process (Walton et al. 2001). CYP1A2, which has been detected only in the liver, and accounts for about 15% of the total cytochromes P450 (CYPs) in the human liver, where its protein content corresponds to 12.7 ± 6.2% of total CYP (Shimada et al. 1994), is responsible for more than 90% of caffeine clearance. The large interindividual variability of CYP1A2 activity influences the disposition of a substrate such as caffeine (Landi et al. 1999) and these variations may be due to factors such as gender, race, genetic polymorphisms, and exposure to inducers (Rasmussen et al. 2002). The molar ratios of metabolites of caffeine used as an index of CYP1A2 activity in populations are distributed according to bimodal or trimodal distributions, and normal or unimodal distributions have also been suggested (Landi et al. 1999). At least two distinct liver CYP enzymes with differing substrate affinities have the potential to catalyze caffeine N-demethylations and C8-hydroxylations in vitro but at the low concentrations routinely encountered in vivo, participation by the high-affinity site is expected to predominate (Campbell et al. 1987a). In vivo and in vitro evidence suggests that CYPs involved in the demethylation pathways are distinct from isozymes involved in the hydroxylation pathways, but these different isozymes seem to be under common regulatory control (Robson 1992).

The ratios of urinary concentrations of AFMU to 1MX or AFMU to 1MX plus 1MU (Grant et al. 1984) or the corresponding ratios with the complete conversion of AFMU into 5-acetylamino-6-amino-3-methyluracil (AAMU) (Tang et al. 1986; Kilbane et al. 1990) give markers of acetylator status in man. In addition, the ratio of 1MU to 1MX represents an index of xanthine oxidase, that of 1,7DMU to paraxanthine represents an index of microsomal 8-hydroxylation, that of AFMU plus 1MX plus 1MU to paraxanthine represents an index of microsomal 7-demethylation, and the caffeine metabolic ratio, AFMU plus 1MX plus 1MU to 1,7DMU, reflects microsomal 3-demethylation and also systemic caffeine clearance as well as polycyclic aromatic hydrocarbon-inducible CYP activity (Arnaud and Enslen 1992; Campbell et al. 1987a, b). The molar ratio of paraxanthine to caffeine in urine taken 3–4 h after caffeine administration was proposed as an alternative to evaluate hepatic CYP1A2 activity (Kadlubar et al. 1990). The ratio of paraxanthine to caffeine or the ratio of paraxanthine plus 1,7DMU to caffeine, has been used as an indicator of CYP1A2 activity and the AFMU-to-1MX ratio indicated *N*-acetyltransferase 2 (NAT2) activity; both appear to be polymorphically distributed in human populations with slow and rapid phenotypes (Butler et al. 1992). These ratios have been tested and validated (Spigset et al. 1999a; Butler et al. 1992; Tang et al. 1994; Carrillo et al. 2000; Doude van Troostwijk et al. 2003b; Derby et al. 2008) but a more detailed analysis of the literature is beyond the scope of this review. No association was found between acetylation activity and sex; race; age; education; smoking; physical activity; weight; consumption of coffee, alcohol, red meat, processed meat, and cruciferous vegetables; or use of estrogens, after taking the genotype into account (Le Marchand et al. 1996). Drug cocktails have been developed for simultaneous phenotyping of CYP1A2, CYP2A6, CYP2C9, CYP2E1, CYP2C19, CYP2D6, CYP3A, NAT2, and xanthine oxidase (Streetman et al. 2000; Zhu et al. 2001; Christensen et al. 2003; Fuhr et al. 2007; Ryu et al. 2007).

CYP1A2 was responsible for caffeine 3-demethylation and paraxanthine 7-demethylation and may catalyze virtually all reactions related to caffeine and its metabolites. Caffeine biotransformation by CYP1A2 averaged 81.5% for paraxanthine, 10.8% for theobromine, and 5.4% for theophylline, while CYP2E1 had major influences on the formation of theophylline and theobromine (Gu et al. 1992). Whereas CYP1A2 accounts for the high-affinity component of all three human hepatic caffeine N-demethylations, CYP2E1 appears to be the main enzyme involved in the low-affinity components of caffeine N1- and N7-demethylation, while 8-hydroxylation of caffeine was suggested to be catalyzed predominantly by a CYP3A isoform (Tassaneeyakul et al. 1994). CYP2D6-Met also had high intrinsic clearance and catalyzed caffeine demethylation and 8-hydroxylation. CYP2E1 played a less important role in vitro and CYP3A4, which predominantly catalyzed 8-hydroxylation, may contribute significantly to the in vivo formation of 1,3,7TMU, owing to its high abundance in human liver. Thus at least four CYP isoforms are involved in caffeine metabolism at 3 mmol/L caffeine concentration, but at concentrations below 0.1 mmol/L, CYP1A2 and CYP1A1 are the most important isoenzymes (Ha et al. 1996).

In humans no gender differences in caffeine metabolism were observed from urinary metabolite patterns or metabolite ratios (Grant et al. 1983), although higher activity of CYP1A2 has been shown in men than in women (Landi et al. 1999). This general conclusion is supported by other studies (Vistisen et al. 1992; Campbell et al. 1987b; Kall and Clausen 1995; Rasmussen et al. 2002; Chung et al. 2000; Ghotbi et al. 2007; Begas et al. 2007; Djordjevic et al. 2008). During pregnancy, the excretion of 1MX and of 1MU were increased (Scott et al. 1986). This observation is in agreement with a caffeine study showing a significantly increased hydroxylation activity during pregnancy. Late pregnancy was also characterized by a decrease in CYP1A2, xanthine oxidase, and acetyltransferase activities (Bologa et al. 1991). In nonsmoking pregnant women and in smoking women using oral contraceptives, the caffeine metabolic ratio was reduced by 29 and 20%, respectively, compared with a control group, demonstrating an inhibition of CYP1A2 (Vistisen et al. 1991). Metabolic ratios for the CYP1A2 index during early, middle, and late pregnancy were significantly lower than the ratio after delivery ($P < 0.0001$). A lower metabolic ratio for NAT2 was also observed during pregnancy ($P < 0.01$) but there was no significant difference in the metabolic ratios for xanthine oxidase during pregnancy and after delivery (Tsutsumi et al. 2001). Oral contraceptive users had lower ($P < 0.05$) ratios of paraxanthine 7-demethylation to 8-hydroxylation products than women not taking oral contraceptives (Campbell et al. 1987b). Upon administration of oral contraceptives, the urinary excretion of caffeine, paraxanthine, and 1,7DMU was increased at the expense of 1MX, 1MU, and the acetylated metabolites AFMU and AAMU. A 33% decrease of the caffeine metabolic ratio was reported in women using oral contraceptives (Kalow and Tang 1991a).

The caffeine ratio AFMU plus 1MU plus 1MX to 1,7DMU in a 6-h urine sample was significantly higher in women not taking oral contraceptives compared with women taking oral contraceptives, thus confirming that CYP1A2 is inhibited by oral contraceptives (Rasmussen et al. 2002). As a marker of CYP1A2 activity, the plasma caffeine-to-paraxanthine ratio was 2.8 times higher ($P < 0.001$) in the oral contraceptive (ethinylestradiol) users than in the control subjects, suggesting an inhibition of CYP1A2 activities (Granfors et al. 2005).

Analysis of caffeine metabolites revealed two interethnic variations, one pertaining to the acetylation polymorphism and the other consisting of a difference in paraxanthine excretion, which might indicate an ethnic difference in renal function (Kalow 1986). A nonsignificant higher proportion of rapid acetylator was observed in the Oriental compared with the European population and a 6.3-fold range variation was observed (Kalow and Tang 1991a). The NAT2 activity showed a typically bimodal distribution with 47% fast acetylators and 53% slow acetylators, consistent with a Danish population (Vistisen et al. 1992). However, only 11.0% of Japanese men and women residents of Kyushu were slow acetylators (Saruwatari et al. 2002). With use of the urinary caffeine metabolic ratio AFMU to 1X (less than 0.6) to classify subjects as slow acetylators, a prevalence of this phenotype of 92.2 and 74.5% was noted in two studies in a population of Minnesota Hmong, but a significant discordance between phenotype and genotype was identified

(Straka et al. 2006). The combined low-risk phenotype (slow CYP1A2/rapid NAT2) was more common in blacks than in whites (25 vs. 15%, $P < 0.02$), but there were no significant racial differences in slow and rapid CYP1A2 phenotypes, and in the combined slow NAT2/rapid CYP1A2 phenotype (Muscat et al. 2008). The ratios reflecting CYP1A2 activities were described as log-normal-distributed (Vistisen et al. 1992). CYP1A2 activity was not normally distributed in subjects from Arkansas, Italy, and China and appeared trimodal with arbitrary designation of slow, intermediate, and rapid phenotypes, which ranged from 12–13% slow, 51–67% intermediate, and 20–37% rapid (Butler et al. 1992). Slow and intermediate CYP1A2 metabolizers represent about 50% of Caucasians, while their frequency in Japanese subjects seems to be much lower (Landi et al. 1999). The distribution of CYP1A2 measured with the plasma paraxanthine-to-caffeine ratio in a Chinese population showed a 16-fold variation of CYP1A2 activity and a coefficient of variation of 62.9%. Nonnormal CYP1A2 activity ($P < 0.001$) with a bimodal distribution ($P < 0.01$) was observed. The percentage of poor metabolizers was 5.24% in this Chinese population (Ou-Yang et al. 2000). The metabolic ratio for CYP1A2 was not polymorphic in Japanese subjects and decreased 1,7DMU formation from caffeine in poor metabolizers of CYP2A6 appeared to affect the metabolic ratio used for the assessment of CYP1A2 activity (Saruwatari et al. 2002). CYP1A2 enzyme activity determined using the 4-h plasma paraxanthine-to-caffeine ratio was 1.54-fold higher in Swedes than in Koreans ($P < 0.0001$) despite them having the same CYP1A2 genotype, smoking habit, and oral contraceptive use. Four known (CYP1A2*1A, CYP1A2*1D, CYP1A2*1F, and CYP1A2*1L) and two novel (CYP1A2*1V and CYP1A2*1W) haplotypes were found (Ghotbi et al. 2007). The mean CYP2A6 activity measured by the caffeine metabolite ratio (1,7DMU to paraxanthine) was significantly lower in Japanese Americans than in native Hawaiians ($P = 0.001$ and $P < 0.0001$, respectively) or whites ($P < 0.0001$) (Derby et al. 2008). The xanthine oxidase index was not different between Chinese and European populations and showed a 1.7-fold range variation (Kalow and Tang 1991a). The ratios reflecting xanthine oxidase activities were normally distributed (Vistisen et al. 1992). Low xanthine oxidase activities exist in a Japanese population corresponding to 11% of the subjects with a mean urinary uric acid concentration 53% lower than that of the other subjects ($P < 0.0001$) (Saruwatari et al. 2002).

As noted in Sect. 2.5, drug intake is expected to alter caffeine metabolism when competitive inhibition or induction of the relevant enzymes is observed. Such interactions can involve smoking and Chinese herbal medicines, but St John's wort, garlic oil, *Panax ginseng*, and *Ginkgo biloba* showed no effect on CYP1A2 activity measured from the paraxanthine-to-caffeine serum ratio (Gurley et al. 2002). As expected, allopurinol treatment caused a specific, dose-dependent inhibition of the conversion of the caffeine metabolite 1MX to 1MU, thus validating an in vivo index of xanthine oxidase activity in man (Grant et al. 1986; Lelo et al. 1989). The proton pump inhibitor omeprazole induces hepatic CYP1A2 activity, as shown by the increased N3-demethylation of [3-Me-^{13}C]caffeine. In extensive metabolizers there was a 8–17% CYP1A2 induction after administration of

40 mg omeprazole and a 25–32% increase ($P < 0.002$) was observed with 120 mg/day. In poor metabolizers a higher increase of 40–41% was observed and there was a good correlation between the caffeine breath test and plasma caffeine clearance (Rost and Roots 1994).

2.6 Sources of Variation in Caffeine Pharmacokinetics and Metabolism

Caffeine metabolism is affected by genetic determinants, age, pregnancy, diet, and lifestyle such as smoking, environmental factors, medications, including contraceptive use, and disease states.

2.6.1 Age

The pharmacokinetics of caffeine studied in young dogs aged 1 day, and 7, 14, and 30–45 days and adult dogs showed that the plasma elimination half-life was 47.5 ± 5.35 h in 1-day-old puppies, as opposed to 6.66 ± 0.85 h in adult dogs. A rapid decrease in plasma half-lives occurred during the first 2 weeks of life and at about 14 days of age the caffeine plasma half-life was similar to that of adults. The volume of distribution was greatest and the total body clearance was smaller in the 1-day-old dogs (Warszawski et al. 1977). The time needed to reach the plateau of the cumulative excretion of radioactivity in the urine decreased with age. All these results are consistent with the slow plasma elimination of caffeine in the newborn as compared with the adult (Warszawski et al. 1982). The elimination of caffeine is impaired in neonates because of their immature metabolizing hepatic enzyme systems (Pons et al. 1988) and plasma half-lives of 65–103 h in neonates have been reported, decreasing rapidly to 14.4 h in 3–5-month-old infants, 2.6 h in 5–6-month-old infants, and 3–6 h in adults and the elderly. The clearance of 31 mL/kg/h in 1-month-old infants increases to a maximum of 331 mL/kg/h in 5–6-month-old infants, and is 155 mL/kg/h in adult subjects. A mean distribution volume of 0.7 L/kg (0.5–0.8 L/kg) was found in newborn infants, adult subjects, or aged subjects. The pharmacokinetics of caffeine in healthy young men aged 20.5 ± 2.0 years and in healthy elderly men aged 71.2 ± 3.9 years showed that T_{max}, C_{max}, and caffeine bioavailability were essentially identical. The apparent volume of distribution was significantly lower but the larger clearances and the greater elimination rate constant in the elderly subjects were not significant because of the wide intersubject variability as shown in the caffeine half-lives ranging from 2.27 to 9.87 h. In this study, pharmacokinetic parameters of caffeine were similar in young and elderly men (Blanchard and Sawers 1983b). The renal clearance of caffeine calculated following both oral and intravenous doses of caffeine in young and elderly, healthy human volunteers showed a highly statistically significant positive correlation ($P < 0.001$) between the renal clearance of both unbound and total clearance of caffeine and the mean urine flow rate (Blanchard and Sawers

1983c). Thus, the comparative pharmacokinetics in the young and elderly shows no significant differences in half-life, suggesting that aging does not alter caffeine elimination in contrast to the rat model, where an age-dependent increase of caffeine half-life has been observed.

2.6.2 Gender and Hormones

The caffeine apparent volume of distribution and the caffeine elimination rate constant were influenced by the different modes of maternal caffeine ingestion during the premating and pregnant periods (Nakazawa et al. 1985). The disposition of caffeine given as single oral dose of 5 and 25 mg/kg to 20-day pregnant and nonpregnant rats showed a significantly longer plasma half-life in the pregnant than in the nonpregnant rats for the highest dose, while the elimination rate was similar at the lowest dose (Abdi et al. 1993). In pregnant rabbits, the pharmacokinetics of caffeine received by continuous intravenous infusion through 29 days of gestation exhibited increased plasma concentrations of caffeine and its major metabolite paraxanthine in the last half of gestation. Rabbits exhibited caffeine AUC at 29 days of gestation that were 85–165% greater than those observed before mating, suggesting that the elimination of caffeine is diminished in late gestation in the rabbit (Dorrbecker et al. 1988a).

Similarly, the caffeine half-life was prolonged during the last trimester in pregnant women and returned to the prepregnant value a few weeks after they had given birth (Arnaud 1993a). From a cohort study of normal third-trimester pregnancies with significant “high”(H) and “low”(L) long-term maternal caffeine ingestion ($P < 0.0002$), it was shown that the maternal serum caffeine levels in group H were significantly higher ($P < 0.05$) at each week of gestation than those in group L and increased until 36 weeks ($P < 0.0039$) but did not increase significantly in group L until 40 weeks (Devoe et al. 1993). The half-life of caffeine increases during pregnancy, reaching 11.5–18 h by the end of pregnancy, leading to an accumulation with regular daily consumption as neither the fetus nor the placenta can metabolize caffeine (Grosso and Bracken 2005). Comparisons of the follicular and luteal phases revealed that systemic clearance of caffeine was slower in the luteal phase, an effect related to the proximity to onset of menstruation and to levels of progesterone although the half-life did not differ (Lane et al. 1992). All pharmacokinetic parameters were similar between women taking no oral contraceptives and men except for the volume of distribution, which was significantly larger in the women ($P < 0.05$) (Patwardhan et al. 1980), and gender had no significant effect on caffeine pharmacokinetics (McLean and Graham 2002). Oral contraceptive use has been shown to double the caffeine half-life (Abernethy and Todd 1985; Patwardhan et al. 1980; Arnaud 1993a). As compared with women taking no oral contraceptives, the half-life of caffeine was significantly prolonged in women taking oral contraceptives from 6.2 ± 1.6 to 10.7 ± 3.0 h ($P < 0.001$), showing impaired elimination of caffeine. Women taking oral contraceptives had a significantly lower total plasma clearance (0.79 ± 0.21 vs. 1.3 ± 0.35 mL/min/kg)

and free clearance (1.12 ± 0.28 vs. 1.97 ± 0.57 mL/min/kg) than women not taking oral contraceptives, while the volumes of distribution and plasma binding were similar in both groups (Patwardhan et al. 1980). Oral contraceptive steroids increased twofold the residence time of caffeine in young women. The effect was already observed during the first cycle 2 weeks after starting to take oral contraceptive steroids and was slightly increased in the second cycle, after 6 weeks on oral contraceptive steroids (Rietveld et al. 1984). The effect of chronic administration of low-dose estrogen-containing (less than 50 μg estrogen) oral contraceptives on the pharmacokinetics of caffeine confirmed that the elimination half-life of caffeine was prolonged to 7.88 h versus 5.37 h in the controls, as a result of impairment of the plasma clearance of caffeine (1.05 vs. 1.75 mL/min/kg, respectively), with no change in the apparent volume of distribution (Abernethy and Todd 1985). The plasma caffeine clearances and elimination half-lives after ingestion of a guarana-containing supplement were lower (0.34 ± 0.01 vs. 0.99 ± 0.41 mL/min kg) and longer (15.5 ± 0.3 vs. 5.6 ± 1.7 h), respectively, in subjects taking oral contraceptives (Haller et al. 2002).

2.6.3 Physical Exercise

The effect of moderate exercise (30% of maximum O_2 uptake) on the kinetics of caffeine in healthy volunteers showed that exercise significantly raised C_{max} and reduced both the half-life and the volume of distribution (Collomp et al. 1991), but other studies show minimal effects on caffeine pharmacokinetics (Kamimori et al. 1987; McLean and Graham 2002).

2.6.4 Obesity

Obesity increases the apparent volume of distribution (69.9 ± 5.9 vs. 43.6 ± 2.8 L; $P < 0.001$), with no significant change in clearance and a trend toward a prolonged elimination half-life (Abernethy et al. 1985). At rest, obese subjects (more than 30% body fat) had a significantly higher absorption rate constant (K_a 0.0757 vs. 0.0397/min), a lower elimination rate constant (K_e 0.0027 vs. 0.0045/min), and a longer serum half-life (4.37 vs. 2.59 h) in comparison with lean subjects. In exercise as well as at rest, lean and obese subjects had a large difference in the volume of distribution, 43.2 versus 101 L in exercise and 54.1 versus 103 L at rest. Exercise consistently resulted in a decrease in caffeine C_{max} and AUC in obese subjects (Kamimori et al. 1987). In severely obese subjects, the caffeine half-life and oral clearance rate were not altered significantly, but it was confirmed that obese individuals exhibited an increased volume of distribution and this volume was decreased with weight reduction. The effect was more important in females and it was suggested that the caffeine distribution was incomplete into the adipose tissue representing 70–80% excess of body weight in obese subjects (Caraco et al. 1995). After oral administration of caffeine as coffee in obese subjects (body mass index

28.01 ± 0.92) and control subjects, there was no significant difference in the caffeine and theobromine levels in saliva but significantly lower levels of theophylline ($P < 0.05$) and higher levels of paraxanthine ($P < 0.01$) were found in obese subjects, suggesting that obesity alters caffeine metabolism and modifies the urinary metabolite concentration ratios used as indexes of enzyme activities (Bracco et al. 1995).

2.6.5 Drugs

Given the *major* role of the liver in the metabolism *of caffeine and many* drugs*, a few examples of these interactions are described from a very large literature*. Clinical studies have reported frequent drug interactions leading to impaired caffeine elimination and decreased clearance both for caffeine and for its metabolites (Lelo et al. 1989). Traditional medicine as well as supplements prepared from plant extracts may affect caffeine pharmacokinetics. With use of caffeine as a probe drug, the effect of sodium tanshinone IIA sulfonate, a water-soluble derivative of the Chinese medicine Danshen, on the activity of CYP1A2 in humans has been tested on healthy volunteers. CYP1A2 activity monitored by the ratio of paraxanthine to caffeine at 6 h in plasma significantly increased by 41.1%, the AUC of caffeine significantly decreased by 13.3%, and the AUC of paraxanthine significantly increased by 17.4% (Chen et al. 2009a). After administration of St John's wort (Esbericum capsules; 240 mg/day of extract, 3.5 mg hyperforin) or a placebo, no statistically significant differences of the primary kinetic parameter, the AUC of caffeine and paraxanthine, between the placebo group and the St John's wort group were observed (Arold et al. 2005). Interaction between the selective serotonin reuptake inhibitor fluvoxamine (50–100 mg/day) and caffeine (200 mg orally) in healthy volunteers showed a decreased total clearance of caffeine from 107 to 21 mL/min and an increased half-life from 5 to 31 h. The N3-, N1-, and N7-demethylation clearance of caffeine decreased from 46 to 9 mL/min, from 21 to 9 mL/min, and from 14 to 6 mL/min, respectively (Jeppesen et al. 1996). However, fluvoxamine (50 mg/day orally) disposition studied in healthy nonsmoking male volunteers who also received caffeine (200 mg orally) showed no significant correlations between caffeine and fluvoxamine clearance or between the paraxanthine-to-caffeine ratio in serum 6 h after caffeine intake and fluvoxamine oral clearance (Spigset et al. 1999b), in contrast to previous in vitro (Brøsen et al. 1993) and in vivo (Sperber 1991; Jeppesen et al. 1996) studies. Other drugs that may interfere include the antipsychotic drug clozapine (Doude van Troostwijk et al. 2003a), the anti-inflammatory drugs idrocilamide (Brazier et al. 1980a) and rofecoxib (Backman et al. 2006), and tacrine (Fontana et al. 1998). Caffeine metabolism has been shown to be inhibited by quinolone antibiotics. In vitro tests ranked the likelihood of these interactions as follows: enoxacin, 74.9%; ciprofloxacin, 70.4%; nalidixic acid, 66.6%; pipemidic acid, 59.3%; norfloxacin, 55.7%; lomefloxacin, 23.4%; pefloxacin, 22.0%; amifloxacin, 21.4%; difloxacin, 21.3%; ofloxacin, 11.8%; temafloxacin, 10.0%; fleroxacin, no effect. In vivo studies showed that

the likelihood of an interaction with caffeine is as follows: enoxacin > ciprofloxacin = norfloxacin > ofloxacin = lomefloxacin (Fuhr et al. 1992). Among fluoroquinolones, enoxacin and to a lesser extent ciprofloxacin and pefloxacin inhibit the metabolic clearance of caffeine (Kinzig-Schippers et al. 1999; Granfors et al. 2004) and it was suggested to use noninteracting quinolones such as ofloxacin and norfloxacin.

Other antidepressants and drugs for the management of anxiety disorders such as venlafaxine, alprazolam, zolpidem, and trimethadione as well as the wakefulness-promoting agent armodafinil did not significantly alter the pharmacokinetics of caffeine and its metabolites (Amchin et al. 1999; Schmider et al. 1999; Cysneiros et al. 2007; Tanaka et al. 1993; Darwish et al. 2008).

2.6.6 Disease

Several animal models of liver disease show reduced total body clearance of caffeine (Tanaka et al. 1992a, 1995; Schaad et al. 1995; Kokwaro et al. 1993). Similarly, humans with several types of liver disease, including cirrhosis (Wietholtz et al. 1981), noncirrhotic, chronic hepatitis B or C, and subjects with cirrhosis, showed a highly significant reduction in plasma clearance correlating with the severity of the disease ($P < 0.001$) (Park et al. 2003; Tanaka et al. 1992b; Scott et al. 1989). The reduced plasma disappearance rate of caffeine in cirrhotics was related to the delayed formation of paraxanthine (Holstege et al. 1989; Jodynis-Liebert et al. 2004). Chronic consumption of alcohol leading to cirrhosis was shown to increase the caffeine half-life up to 50–160 h (Statland and Demas 1980; Desmond et al. 1980; Renner et al. 1984; Scott et al. 1988). A study performed in patients with decompensated type I and type II diabetes mellitus showed that the caffeine half-life, apparent clearance and distribution volume, and paraxanthine-to-caffeine ratio for the CYP1A2 index were similar to those of controls (Zysset and Wietholtz 1991; Matzke et al. 2000).

2.6.7 Smoking

Although some studies showed no effect (Oliveto et al. 1991), most studies found that caffeine clearance was stimulated by smoking (Brown and Benowitz 1989; Parsons and Neims 1978; Wietholtz et al. 1981; Arnaud and Welsch 1982; Kotake et al. 1982; Caraco et al. 1995; Zevin and Benowitz 1999; Bchir et al. 2006). Cigarette smoking nearly doubles the rate of caffeine metabolism owing to the enzyme-inducing effects of polycyclic aromatic hydrocarbons, known to increase liver enzyme activity (Kalow and Tang 1991b; Parsons and Neims 1978). Multivariate analysis revealed that with disease state, smoking ($P < 0.001$) was a significant predictor of the caffeine breath test, thus showing it to be a valid indicator of plasma caffeine clearance and hepatic function (Park et al. 2003). Cigarette smoking increases the elimination of caffeine, whereas cessation of

cigarette smoking significantly reduces caffeine clearance (Murphy et al. 1988) and changes the pattern of caffeine metabolism (Brown et al. 1988). The time-course changes of CYP1A2 activity measured from the paraxanthine-to-caffeine ratio in plasma after cessation of smoking in heavy smokers showed that the initial caffeine clearance decreased significantly ($P < 0.01$) by 36.1% and the apparent half-life of the CYP1A2 activity decrease was 38.6 h (Faber and Fuhr 2004).

2.6.8 Diet and Alcohol

During the treatment of neonatal apnea, formula-fed infants, compared with breastfed infants, show a nearly threefold increase in the clearance of caffeine. In HepG2 cells, messenger RNA and protein expression of CYP1A1/CYP1A2 were significantly induced by cow-milk-based formula, but not by human milk. The enhanced in vitro CYP1A expression via an AhR-mediated pathway by infant formula but not human milk provides a potential mechanistic basis for the increased caffeine elimination in formula-fed infants (Xu et al. 2005). The caffeine elimination rate constant was low 2 weeks after birth and displayed a significant positive linear correlation with age ($P < 0.001$). A significantly greater elimination rate constant was observed in formula-fed than in breast-fed infants ($P < 0.001$). This occurred concomitantly with a significant increase in the levels of urinary paraxanthine and 1MX ($P < 0.001$), suggesting increased CYP1A2 activity in formula-fed infants. The urinary molar ratio of paraxanthine plus 1MX to caffeine and age strongly predicted the caffeine elimination rate constant ($P < 0.001$) irrespective of feeding type (Blake et al. 2006).

The influence of nutritional status was investigated in elderly institutionalized patients with either malnutrition or adequate nutrition. The plasma paraxanthine-to-caffeine metabolic ratio was similar in both groups and was not correlated to the body mass index, serum albumin, or renal clearance (Hamon-Vilcot et al. 2004). Daily consumption of at least three cups of coffee significantly increased CYP1A2 enzyme activity (Djordjevic et al. 2008). These results confirmed the findings of a previous study showing that multiple ingestions of dietary caffeine (two to seven cups of coffee) in healthy subjects increased the theophylline serum concentrations given as a single oral dose when compared after deprivation of dietary caffeine. The theophylline half-life was prolonged by 32% ($P < 0.01$) and the total body clearance was reduced by 23% ($P < 0.001$) (Sato et al. 1993). When subjects resumed coffee drinking, interindividual variations preclude a clear answer about the time period required for deinduction to occur. However, regular caffeine intake in high doses for 1 week failed to alter caffeine pharmacokinetics (George et al. 1986).

Grapefruit juice beverage consumption decreased the oral clearance of caffeine by 23% and prolonged its half-life by 31% (Fuhr et al. 1993, 1995). The pharmacokinetics of caffeine and its metabolite paraxanthine were affected by the flavonoid quercetin as shown by their significantly decreased AUC (16%) and decreased urinary excretion of paraxanthine (32%) and 1MX (156%), while urinary excretion of 1,7DMU and of 1MU were both increased by 90% (Chen et al. 2009b).

Alcohol intake in amounts commonly consumed significantly prolonged the caffeine half-life by 72% ($P < 0.005$) and diminished the caffeine clearance by 36% ($P < 0.0005$) (George et al. 1986) ,while the AUC for caffeine was significantly higher when caffeine was administered with 0.8 g/kg alcohol (Azcona et al. 1995).

2.7 Metabolites and Metabolic Pathway

Metabolites specific to animal species were identified in urine, such as trimethylallantoin (Arnaud et al. 1986a), sulfur-containing metabolites (Kamei et al. 1975) and *N*-methylurea and *N*,*N*′-dimethylurea (Arnaud 1976), and may be produced by the intestinal flora. These sulfur-containing metabolites of caffeine were detected in the urine of the horse, rabbit, rat, and mouse and were isolated and identified as α-[7-(1,3-dimethylxanthinyl)]methyl methyl sulfoxide, while two other new metabolites were isolated from the urine of the mouse and identified as α-[7-(1,3-dimethylxanthinyl)]methyl methyl sulfide and α-[7-(1,3-dimethylxanthinyl)] methyl methyl sulfone, respectively (Kamei et al. 1975). Bacterial degradation through C8 oxidation results in the formation of 1,3,7TMU, which is further degraded to trimethylallantoin, *N*,*N*′-methylurea and *N*-methylurea (Madyastha and Sridhar 1998). In urine; a larger fraction of 6-amino-5(*N*-formylmethylamino)-1,3-dimethyluracil (1,3,7DAU) was excreted in rat (30%) in contrast with monkey and man (2%) (Latini et al. 1981). When [Me-^{14}C]-1,3,7DAU was administered orally or intravenously to rats, no further metabolites could be found (Arnaud et al. 1983). After identification and quantification in rat urine of 1,3,8-trimethylallantoin (1–14%) (Rao et al. 1973; Arnaud 1976), its formation from caffeine was demonstrated in rat liver slices and all N-demethylation, oxidation to uric acids, and formation of uracil derivatives were also demonstrated in vitro (Arnaud et al. 1986a). In rat liver slices only primary metabolites were detected and N1-demethylation was the most important pathway, with theobromine representing 51% of total dimethylxanthines produced and 1,3,7DAU was an important metabolite, corresponding to 9.7% of total caffeine metabolites (Bienvenu et al. 1990). In mice strains paraxanthine glucuronide was identified, a metabolite not found in other animal species and in humans (Arnaud et al. 1989). In beagle dogs, the most important metabolic pathway of caffeine (2.8% of the dose) was the 7-methyl demethylation to theophylline (8% with paraxanthine) with further metabolism to 1,3DMU (13%), 3-methylxanthine (3MX) (21%), and 1MU (8%) excreted in urine. Minor metabolites were theobromine (5%), 1,3,7TMU (2.5%), 1,7DMU (2%), 1MX (1%), and 7-methyluric acid (7MU) (2.5%) (Aldridge and Neims 1979). In 2-day-old puppies, urinary caffeine metabolites derived, respectively, from paraxanthine, theophylline, and theobromine accounted for 42, 33 and 14%. Between 2 and 22 days of age, this metabolic pattern changed, with metabolites derived from theophylline increasing from 33 to 82% (Aldridge and Neims 1980). The metabolism of [2-^{14}C]caffeine (4 mg/kg intravenously) studied in rabbits showed that the major urinary metabolites were 1MX (22%), 1MU (19%),

7-methylxanthine (7MX) (16%), and paraxanthine (14%), with other minor metabolites such as 3-methyluric acid (3MU) (4.4%), theobromine (4.0%), 1,7DMU (3.9%), 3MX (3.8%), 1,3DMU (2.7%), 1,3,7TMU (2.0%), and theophylline (1.6%), while the uracil derivative AAMU amounted to 4.9% (Beach et al. 1985). After caffeine administration, similar hepatic capacity to clear caffeine was observed, but 7-demethylation was the preferred pathway in sheep and 3-demethylation in cattle, suggesting different species-specific expression of the CYP1A subfamily (Danielson and Golsteyn 1996).

Caffeine metabolism in humans includes multiple and separate pathways with demethylation to dimethylxanthines and monomethylxanthines, C8 oxidation of these methylxanthines into methylurates, and ring opening yielding substituted uracil derivatives. The reverse biotransformation of theophylline to caffeine was first shown in infants but later also in adult subjects. From the metabolic pathways of caffeine (Fig. 1) it is apparent that each metabolite may be derived from more than one precursor and assessment of caffeine demethylations from urinary metabolite profiles is not accurate (Lelo et al. 1986b). In Fig. 2 the various ratios of metabolites that have been used to measure activities of enzymes involved in caffeine metabolism are shown, particularly CYP1A2, NAT2, and xanthine oxidase. The analysis of urinary caffeine metabolites in man shows the presence of uracil derivatives produced from caffeine, 1,3,7DAU (Arnaud and Welsch 1980a), from theobromine, 6-amino-5-(*N*-formylmethylamino)-1-methyluracil (3,7DAU) (Arnaud and Welsch 1979a, 1980a), and from paraxanthine, 6-amino-5-(*N*-formylmethylamino)-3-methyluracil (1,7DAU) (Arnaud and Welsch 1980a). The amount of 1,3,7DAU found in the urine of adult subjects is about 1% of the administered dose, while its excretion increased in the urine of a premature infant in the case of caffeine overload (Gorodischer et al. 1986a). In this study, the 1,3,7DAU identified in urine was of neonatal and not of maternal origin as it was not present in the urine from the infant obtained prior to administration of caffeine. The acetylated uracil derivative AAMU detected in man (Callahan et al. 1982) has not been identified in animal species. Its precursor was detected, isolated, purified, and identified as AFMU, a structure confirmed by chemical synthesis (Tang et al. 1983). AFMU was unstable in the presence of dilute base and/or methanol, giving rise to a deformylated compound, AAMU, which was reported in the literature as a major metabolite of caffeine in man (Arnaud 1980; Arnaud and Welsch 1980a; Callahan et al. 1982). The production and excretion rates of AAMU and AFMU were shown to be related to the acetylation polymorphism (Grant et al. 1983) with a bimodal distribution of the general population into fast and slow acetylators. Paraxanthine is the precursor of AFMU, which accounts for 67% of paraxanthine clearance. The rate of AFMU production and clearance approximates and changes according to the rates for the production of 1MX and 1MU (Yesair et al. 1984), suggesting that its formation occurs through a common precursor of AFMU and 1MX. This intermediate has not yet been identified. A major difference between humans and rats is the total excretion of caffeine and metabolites without demethylation, which amounts to 5 and 42% of the dose administered, respectively (Arnaud and Welsch 1980a; Arnaud 1985). From the analyses of urine metabolites

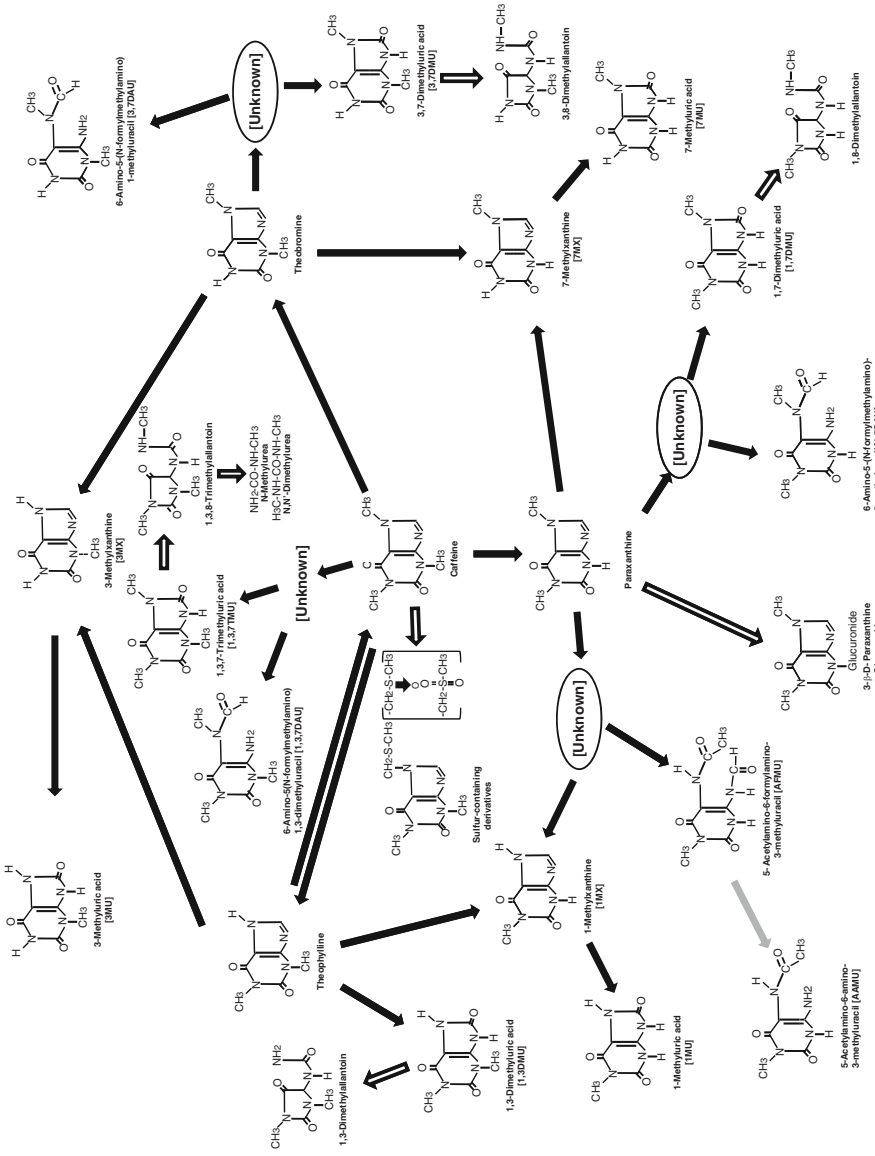

Fig. 1 Metabolic pathways of caffeine, theophylline, theobromine, and paraxanthine in human (⬛) and animals (⇧)

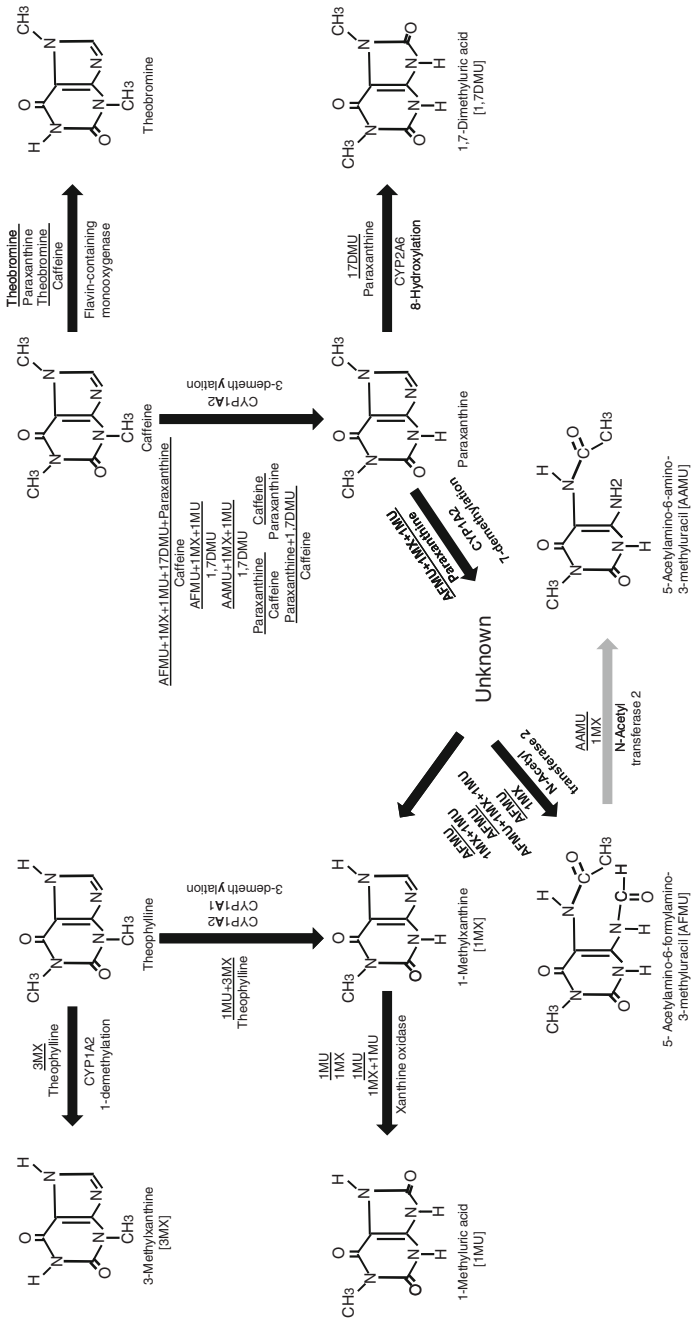

Fig. 2 Metabolite molar ratios measured in urine and plasma used as indexes of enzyme activities

in humans, the quantitative importance of the metabolic pathways through paraxanthine (72%) was the greatest followed by theobromine (20%) and theophylline (8%) (Arnaud and Welsch 1980a, 1982). These results were confirmed where 78 ± 11% of the excreted metabolites were metabolized through the paraxanthine pathway, 14 ± 8% through theobromine, and 9 ± 4% through theophylline. However, the plasma AUC for dimethylxanthines underestimates the formation of paraxanthine, overestimates the formation of theobromine, and gives a similar formation for theophylline from caffeine, when compared from the urinary metabolites (Rodopoulos and Norman 1996). From the plasma AUC of caffeine and each dimethylxanthine, the mean fractional conversion of caffeine to paraxanthine, theobromine, and theophylline was 79.6 ± 21.0, 10.8 ± 2.4, and 3.7 ± 1.3%, respectively (Lelo et al. 1986b). Another study found that paraxanthine accounted for 63 ± 13% of the dimethylxanthines in plasma, theobromine 27 ± 15%, and theophylline 10 ± 2.6% (Rodopoulos and Norman 1996). For demethylation, 3-demethylation represents 52% of all metabolites, 7-demethylation 35%, and 1-demethylation 13% (Arnaud and Welsch 1980a; Yesair et al. 1984). When demethylation pathways are considered from plasma AUC results, paraxanthine, theobromine, and theophylline accounted for 83.9 ± 5.4, 12.1 ± 4.1, and 4.0 ± 1.4%, respectively, of the caffeine demethylations (Lelo et al. 1986b). From clearance values of caffeine and its primary metabolites, it was calculated that approximately 37% of a caffeine dose was biotransformed to paraxanthine (Tang-Liu et al. 1983), a lower value when compared with excreted metabolite. To quantify the total demethylation process, the administration of [1,3,7-Me-^{13}C] caffeine to volunteers and continuous collection of expired $^{13}CO_2$ showed that 21–26% of the total ^{13}C administered was recovered in expired CO_2 over 24 h, corresponding to a mean percentage of demethylation for each methyl group (Arnaud et al. 1980). The quantitative urinary excretion of caffeine metabolites in man and in various animal species, expressed as the percentage of the administered dose, is shown in Table 1. However, large individual variations in urinary metabolite excretion have been reported and the caffeine metabolites recovered, expressed as the percentage of the dose, in young and elderly men showed significantly higher excretion in the elderly for 1,7DMU ($P < 0.05$), 1MU ($P < 0.03$), and 7MU ($P < 0.03$) for both oral and intravenous administration, but lower urine recoveries were observed in young men (Blanchard et al. 1985).

3 Theophylline

3.1 Absorption

Theophylline transfer across rat jejunum in vitro showed that its clearance was directly proportional to the fraction unionized at various pH values (Perry et al. 1984), and there were small but nonsignificant differences in absorptive capacity between the

Table 1 Urinary excretion of caffeine, theophylline, theobromine, and paraxanthine metabolites in human and animals

	Caffeine		Theophylline		Theobromine		Paraxanthine	
	Human	Animals	Human	Animals	Human	Animals	Human	Animals
Caffeine	1.2	2[a], 3[b], 0.9[c], 4.5[d]						
Theophylline	1	0.7[a], 6[b], 1.6[c], 12.5*[d]	16	38[b]				
Theobromine	2	4[a], 8[b], 4[c], 7.5[d]			20	26[a], 53[b], 19.5[c], 50[d]		
Paraxanthine	6.5	14.5[a], 12.5[b], 14.5[c,*d]					11	52[b]
Trimethyluric acid	1.4	4[a], 8[b], 2[c], 4[d]						
Trimethylallantoin		0.4[a], 7[b]						
5-Acetylamino-6-formylamino-3-methyluracil	16	–					20	
5-Acetylamino-6-amino-3-methyluracil	–	5[c]						
6-Amino-5-[*N*-formylmethylamino]-1,3-dimethyluracil	1.2	9.5[a], 21[b]						
1,7-Dimethyluric acid	6	6.3[a], 5[b], 4[c], 3[d]					17	7[b]
6-Amino-5[*N*-formylmethylamino]-3-methyluracil	2.5	1.4[a], 2.5[b]					5	7[b]
1,3-Dimethyluric acid	2.6	7.5[a], 4[b], 2.5[c], 20[d]	47	38[b]				
6-Amino-5[*N*-formylmethylamino]-1-methyluracil	2	5[a], 6[b]			12	44[a], 29[b], 14[c], 10[d]		
3,7-Dimethyluric acid	0.8	1[a], T[b]			1	4[a], 4.5[b], 2[c], 0.5[d]		
Dimethylallantoin		T[b]		<1[b]		T[b]		
1-Methylxanthine	19		1	<1[b]			17	11[b]

		6.3[a], 5[b], 22[c], 1.5[d]							
7-Methylxanthine	7.5	3[a], 2[b], 16[c]			36	12.5[a], 4[b], 49[c]–4.5[d]	5.5		2[b]
3-Methylxanthine	3	2[a], 1[b], 4[c], 31[d]	14	3.5[b]	21.5	5[a], 6.5[b], 11.5[c], 27[d]			
1-Methyluric acid	26.5	8.5[a], 6.5[b], 19[c], 12.5[d]	20	20[b]			19		21[b]
7-Methyluric acid	–	1[a], 0.8[b], 3.5[d]			8.5	8[a], 2[b], 3[c], 6[d]	4.5		T[b]
3-Methyluric acid	0.1	2[a], 0.3[b], 4.5[c]	1	<1[b]	0.6	0.5[a], T[b], 0.8[c], 1[d]			
3-β-D-Paraxanthine glucuronide	–	20[a], 0[b]							9–25[a]
α-[7-(1,3-Dimethylxanthinyl)] methyl methyl sulfoxide	–	T[a–c]							
α-[7-(1,3-Dimethylxanthinyl)] methyl methyl sulfide	–	T[a]							
α-[7-(1,3-Dimethylxanthinyl)] methyl methyl sulfone	–	T[a]							
N-Methylurea	–	T[b]				T[b]			
N,*N*′-Dimethylurea	–	T[b]							

The results are expressed as the percentage of metabolites excreted in urine (at 48 h in human). From Arnaud and Welsch (1980a, b), Callahan et al. (1982), Shively and Tarka (1983), Tarka et al. (1983), Miller et al. (1984), Arnaud (1984, 1985), Beach et al. (1985), Birket et al. (1985), Arnaud et al. (1989), Rodopoulos et al. (1996), and Rodopoulos and Norman (1997).

T traces

[a]Mouse urine (24–36 h)

[b]Rat urine (24 h)

[c]Rabbit urine (36 h)

[d]Dog urine (48 h)

[*]Value of theophylline + paraxanthine

intestinal segments studied (Murray et al. 1993). The rhythmicity in plasma levels found in theophylline disposition was not due to diurnal variation in the passive transport of the mucosa, but may be caused by differences in food intake between morning and evening, in the transit time or gastric emptying, or in the amount or composition of the gastric or intestinal fluid (Tukker and Meulendijk 1991). Exsorption of theophylline from blood to the gastrointestinal tract corresponded to 12–15%, while the extent of the drug excreted into the bile varied from 0.17 to 0.30% (Arimori and Nakano 1988). Rectal absorption of theophylline is slow but complete.

Also in humans, theophylline is rapidly and completely absorbed (Ogilvie 1978; Yesair et al. 1984). It appeared to be almost completely absorbed before it reached the jejunum and the jejunal concentrations were lower than 10% of the maximal duodenal concentrations (Brouwers et al. 2005). The absolute bioavailability of theophylline was investigated by comparing the AUC after intravenous and oral administration of theophylline. The fraction of the dose absorbed averaged 0.99 ± 0.02, thus showing a bioavailability close to 100% (Hendeles et al. 1977) as well as in neonates and young infants (Moore et al. 1989). Food decreased significantly the absorption rate of theophylline, prolonged T_{max}, and decreased C_{max}, but the AUC was slightly but not significantly smaller, indicating that theophylline bioavailability was not modified (Jonkman et al. 1985). Oral administration of activated charcoal is a well-established therapy for treatment of theophylline intoxication (Cooling 1993).

3.2 Distribution

Plasma theophylline concentrations in guinea pigs could be quantitatively described by a two-compartment model with nonlinear elimination kinetics and individual volume distribution of theophylline at each dose (Sato et al. 2007). Protein binding in blood was $48.8 \pm 6.2\%$ in the rats (Ingvast-Larsson et al. 1992). The theophylline dose required to achieve the narrow therapeutic concentrations (10–20 mg/mL) varies among subjects, largely because of differences in metabolism. Another important pharmacokinetic parameter is protein binding. Theophylline binds mainly to albumin and the protein binding of approximately 50% was shown to be nonlinear (Fleetham et al. 1981; Trnavská 1990) ,with little variations in healthy subjects but important changes for physiological (Shaw et al. 1982) and disease (Lesko et al. 1981; Siegel et al. 1990; Korrapati et al. 1995) states. Measured saliva levels allow predictions of the unbound serum theophylline levels. The therapeutic range for saliva, which corresponds to the accepted total serum concentration range of 10–20 μg/mL, is approximately 5.55–11.3 μg/mL (Blanchard et al. 1992).

Recovery of theophylline is much less than that of caffeine in brain, liver, muscle, and adipose tissue (Ståhle 1991), reflecting the lower lipid solubility of theophylline. Lower theophylline concentrations were found in the brain (91 μM) than in other tissues (120 μM) and this rate of penetration into the brain extracellular

space was higher for caffeine than for theophylline (Ståhle et al. 1991). With microdialysis methods applied in anesthetized rats, striatum-to-blood ratios at the steady state of approximately 0.5 were shown (Sjöberg et al. 1992). These results were confirmed and compared with fetal brain AUC values of theophylline; those found in the brains of adults were lower compared with those found in plasma after a dose of 25 mg/kg, suggesting that theophylline might be selectively excluded from the adult brain (Wilkinson and Pollard 1993). Theophylline crosses the placenta and distributes in the organs of the rat fetus and the pregnant animal, except for the brain, where the exposure of the fetal brain was twice that of the adult brain (Arnaud et al. 1982a). Placental clearance of theophylline averaged 0.62 mL/min in the rabbit but it was difficult to extrapolate these results as human and rabbit placentas are structurally dissimilar (Omarini et al. 1991).

3.3 Excretion

There were no significant differences in the elimination and metabolism of [8-^{14}C] theophylline when given orally or intravenously to rats. Fecal excretion amounted to 5 ± 3% of the dose after 7 h and increased to 18 ± 2% after 24 h. About 25% of the dose was secreted in the bowels (Arnaud and Welsch 1980b; Arnaud et al. 1982a, b). After 1 day, 70 ± 7% of the dose was excreted in urine and 6 ± 1% in CO_2 and less than 1% remained in the body (Arnaud and Welsch 1980b). In pregnant rats, labeled caffeine was found in the fetus and only traces were detected in the urine. At the 18th day of pregnancy, unchanged theophylline corresponded to 70 ± 10% of urine activity, suggesting impaired metabolism when compared with 35 ± 3% in nonpregnant rats (Arnaud and Bracco 1981). Theophylline in humans is completely absorbed and fecal excretion has not been reported.

In premature infants with postconception ages of 28–42 weeks, the urinary percentages of unchanged theophylline decreased from 61 to 43%, respectively, suggesting an increased theophylline metabolism into 1,3DMU with age (Tserng et al. 1983). In 10–12-year-old asthmatic children, the percentage of unchanged theophylline excreted in the urine was 11.6 ± 1.75%. Metabolites found in urine in addition to theophylline were 3MX, 1,3DMU, and 1MU (Monks et al. 1979; Wijnands et al. 1990). Theophylline was shown to be extensively reabsorbed in the renal tubule and its renal clearance was highly urine flow dependent and urinary excretion varied with urine output (Tang-Liu et al. 1983).

3.4 Pharmacokinetics

In rats, the plasma concentration decayed according to a first-order process with an apparent half-life of about 4 h, but after 4–8 h the slope of the curves declined, resulting in elimination half-lives of about 70 min, a value similar that for lower

doses. The AUC increased disproportionately with dose, indicating capacity-limited elimination, but there was no capacity-limited elimination of 1,3DMU and 1MU with the dose. These results showed that linear pharmacokinetics of theophylline in rats can be applied only to doses not exceeding 10 mg/kg (Teunissen et al. 1985). The plasma theophylline concentrations in rat declined in a monoexponential manner, while those of 1MU and 1,3DMU declined in a biexponential manner upon their injection. The total body clearances of the metabolites were fourfold to sixfold larger and their distribution volumes were 40–50% smaller than that of theophylline (Kuh and Shim 1994). The pharmacokinetics of theophylline were investigated in Cyp1(+/+) wild-type mice, Cyp1a1(−/−) and Cyp1a2(−/−) knockout mice, and humanized hCYP1A1_1A2 mice lacking either the mouse Cyp1a1 or the mouse Cyp1a2 gene. The half-life of elimination from plasma was more than 4 times longer in Cyp1a2(−/−) mice than in Cyp1(+/+) mice. In humanized hCYP1A1_1A2 mice lacking the mouse Cyp1a2 gene, the half-life of elimination from plasma was 2–3 times longer than that in Cyp1(+/+) mice (Derkenne et al. 2005). A pharmacokinetics study conducted in dogs showed the bioequivalence of the two injectable forms containing theophylline and aminophylline (ethylenediamine salt of theophylline) and thus the lack of influence of ethylenediamine on the pharmacokinetics of theophylline (Kawai et al. 2000).

The demethylation of theophylline at high concentrations shows biphasic kinetics in the production of individual metabolites with human microsomes (Campbell et al. 1987a). In children with chronic asthma receiving two dosage levels of theophylline, the steady-state serum concentrations increased to a greater degree than predicted with a significantly lower clearance at the higher dose ($P < 0.02$). These results showed the nonlinear nature of the relationship between dose and theophylline serum concentration in these children with asthma (Weinberger and Ginchansky 1977). Theophylline elimination from blood in a 10-month-old female acutely intoxicated had a half-life of 10.0 h, an elimination that was anomalously long for a child of this age (Jarboe et al. 1986). Theophylline pharmacokinetics in asthmatic patients of 8–18 years of age showed that C_{max} of 8.4 ± 1.7 mg/L occurred 2.2 h after oral ingestion, with a mean serum half-time for theophylline of 5.8 ± 1.7 h (Becker et al. 1984). The volume of distribution of theophylline depends primarily on age; it is twofold greater in newborns than in adults (Tröger and Meyer 1995). These results were confirmed in healthy male volunteers with total plasma clearances of theophylline of 0.93 mL/min/kg, unbound plasma clearances of 1.61 mL/min/kg, half-lives of 6.2 h, a volume of distribution at steady state of 0.44 L/kg, and an unbound volume of distribution of 0.77 L/kg (Lelo et al. 1986a). Studies have established relationships between renal clearance and urine flow rate for caffeine and theophylline (Trang et al. 1985). Theophylline frequently exhibits nonlinear pharmacokinetics with a relatively large intrapatient variability in clearance over time (Pan et al. 2000). A study confirmed the intrasubject variability reported for theophylline clearance in healthy male volunteers but no significant dose dependency was observed for doses of 1 and 6 mg/kg (Fleetham et al. 1981).

3.5 Metabolism

Several CYP isoenzymes, including CYP1A2, CYP2E1, and CYP3A4, are involved in the hepatic metabolism of theophylline (Pan et al. 2000). Theophylline has (as caffeine) been used as a marker of CYP1A2 activity (Obase et al. 2003). In human adults, approximately 90% of theophylline is metabolized in the liver by CYPs, while unchanged theophylline is excreted via the kidneys (Tröger and Meyer 1995). CYP1A is responsible for theophylline N-demethylation to 3MX and 1MX (Sarkar and Jackson 1994). The positive relationship between clearance of 1MU and of 3MX in both smokers and nonsmokers ($P < 0.001$) suggests that the two N-demethylation pathways for theophylline metabolism are under common regulatory control and involve a CYP distinct from that mediating 8-hydroxylation of theophylline to 1,3DMU (Grygiel and Birkett 1981). Theophylline is metabolized by 8-hydroxylation to 1,3DMU, which accounts for about half of the clearance of the drug in humans (Ogilvie 1978), and by N-demethylation to 3MX and 1MX. Although theophylline 8-hydroxylation is catalyzed by several CYP subfamilies (Zhang and Kaminsky 1995; Gu et al. 1992; Sarkar et al. 1992), CYP1A2 is reported to play a major role only at lower substrate concentrations (Zhang and Kaminsky 1995). A 30-fold individual difference was observed for the 1MU plus 3MX to theophylline ratio in patients receiving theophylline therapy, and in healthy volunteers a 70-fold difference was found for the 1MX plus 1MU plus AFMU to 1,7DMU ratio. The CYP1A2 activities were not significantly influenced by CYP1A2*1C or CYP1A2*1F polymorphism, suggesting that these CYP genotypes are not major factors for the variability of CYP1A2 activity. The CYP1A2*1K haplotype seems to show a very low frequency in this Japanese population (Takata et al. 2006). Pretreatment in rats with an inhibitor or inducer of CYPs such as troleandomycin, 3-methylcholanthrene, orphenadrine or dexamethasone suggested that theophylline was metabolized via CYP1A1/CYP1A2, CYP2B1/CYP2B2, and CYP3A1/CYP3A2, and that 1,3DMU is primarily formed via CYP1A1/CYP1A2, and possibly CYP3A1/CYP3A2 (Yang et al. 2008).

Theophylline was metabolized in cultured hepatocytes and in liver slices of young and adult rats into 1MU, 1MX, 1,3DMU and/or 3MX, caffeine, a uracil derivative, and two unknown polar compounds. Although the same metabolites were identified in young and adult rats, the development pattern was not uniform and formation of caffeine from theophylline was not dependent on a lack of activity of other pathways. Preincubation with caffeine or theobromine inhibited theophylline metabolism (Gorodischer et al. 1986b). In human liver microsomes, the formation of 3MX, 1MX, and 1,3DMU from theophylline was reported and the two demethylation pathways seemed to be performed by the same enzyme (Robson et al. 1988). In addition, α-naphthoflavone inhibited theophylline demethylations, whereas 8-hydroxylations were generally less inhibited (Campbell et al. 1987a). In microsomes prepared from different human livers, the formation of 3MX and 1MX correlated best with amounts of the immunoreactive protein HLd (P-IA2) ($P < 0.05$), whereas formation of 1,3DMU correlated with the microsomal content

of HLp (P-IIIA3) and HLj (P-IIE1). In immunoinhibition experiments, incubations conducted with a polyclonal antirat P-c/d antibody, the formation of all three theophylline metabolites was significantly inhibited ($P < 0.05$). However, addition of isoform-specific antirat-CYP-d antibodies to the microsomal mixture significantly and selectively inhibited 1-N-demethylation, with little inhibition of 3-N-demethylation or 8-hydroxylation (Sarkar et al. 1992). 1MX seemed to be mediated by CYP1A1/CYP1A2 and 3MX specifically by CYP1A2 (Sarkar and Jackson 1994). CYPs expressed in human B-lymphoblastoid cell lines showed that at high theophylline concentration (10 mM) four CYPs (CYP1A1, CYP1A2, CYP2D6, CYP2E1) catalyzed the metabolism of theophylline, but the highest affinity was for the CYP1A subfamily. CYP2E1, responsible for a relatively high intrinsic clearance by 8-hydroxylation, may be the low-affinity high-capacity isoform involved in theophylline metabolism. The affinity of theophylline for CYP1A1 was comparable with that of its homologue CYP1A2 and when induced, the participation of CYP1A1 in theophylline metabolism may be important. CYP2D6 played only a minor role and CYP3A4 was not active in the in vitro metabolism of theophylline. These results confirm the major role of CYP1A2 in theophylline metabolism and explain why the elimination kinetics of theophylline in vivo are nonlinear (Ha et al. 1995). In microsomes, at low theophylline concentrations the metabolism of theophylline to 1,3DMU was catalyzed primarily by CYP1A2, while at high substrate concentrations CYP2E1 was primarily responsible for 1,3DMU formation. At theophylline concentrations achieved in vivo, its metabolism must thus be catalyzed primarily by CYP1A2 (Zhang and Kaminsky 1995). In human, rabbit, and rat liver microsomes 1,3DMU accounted, respectively, for 59, 77, and 94% of the total metabolites formed. In both human and rabbit liver microsomes the N-demethylation of theophylline to 1MX accounted for 20% of the total metabolites formed. In human microsomes N-demethylation of theophylline to 3MX accounted for 21% of theophylline metabolism, but it was a minor pathway in rabbit and rat microsomes (McManus et al. 1988).

3.6 Sources of Variation in Theophylline Pharmacokinetics and Metabolism

Age. Differences in the half-life and total clearance were found among the age groups with a linear correlation between age and the clearance of theophylline (Kearns et al. 1986). The average mean residence time of theophylline was significantly longer in 20-month-old rats than in 2- and 14-month-old rats. A greater elimination rate constant was observed in 14-month-old rats and the apparent volume of distribution decreased from 0.71 to 0.57 L/kg in the 2- and 20-month-old rats, respectively (Jung and Nanavaty 1990). The ability of the rat fetus to methylate theophylline into caffeine was demonstrated when [8-^{14}C] theophylline was administered to pregnant rats (Arnaud et al. 1982a, b). However, the biotransformation of theophylline to caffeine reported for human neonates and the rat fetus was not observed in neonatal piglets (Kearns et al. 1986).

In premature neonates, weighing less than 1,500 g at birth, and under 32 weeks of gestational age, theophylline clearance was lower (12 mL/h/kg) and the volume of distribution (0.8–0.9 L/kg) was higher than previously reported for less premature neonates, term babies, and older children (Lee et al. 1996). The weight-normalized value of the volume of distribution in premature neonates during the first week of life was 0.63 L/kg (du Preez et al. 1999). In contrast to older children and adults, in whom theophylline disposition follows zero-order kinetics at high concentrations, a monoexponential function best described theophylline elimination in the premature newborn, with half-lives ranging from 24.7 to 36.5 h and estimated clearance ranging from 0.02 to 0.05 L/kg/h (Lowry et al. 2001). In premature neonates, only unchanged theophylline and caffeine were found in urine, indicating the absence of oxidative pathways for theophylline metabolism. In both adults and children, there was high positive correlation between urinary excretion of 3MX and 1MU. Both 3MX and 1MU correlated negatively with urinary excretion of 1,3DMU (Grygiel and Birkett 1980). The metabolism of theophylline in premature infants showed that the urinary percentages of unchanged theophylline decreased from 61% at a post-conception age of 28–32 weeks to 43% at 38–42 weeks. This increased metabolism of theophylline is explained by the production of 1,3DMU (20–34%). It was hypothesized that methylation of theophylline to caffeine is equally active in adults and premature infants and the absence of caffeine in adults is due to the maturing caffeine-metabolizing enzymes (Tserng et al. 1983).

Postnatal age was the most powerful predictor for theophylline half-life in the neonatal period, while gestational age, duration of treatment, and weight did not correlate significantly with any pharmacokinetic parameters (Dothey et al. 1989). Theophylline clearance reached adult values at 55 weeks of postconceptional age and the disappearance of serum caffeine concentrations and the maturation of theophylline clearance were primarily related ($P < 0.001$) to development of the demethylation pathway to 3MX. Postconceptional age was the major factor ($P < 0.001$) explaining the interpatient variability in theophylline clearance (Kraus et al. 1993). The total clearance of theophylline was 87–100 mL/h/kg in children and 57 mL/h/kg in adults, with important interindividual differences in the biological half-life (1.42–7.85 h) and a higher elimination rate constant (0.49 ± 0.30/h) in the children (Ellis et al. 1976; Gardner and Jusko 1982; Kolski et al. 1987; Berdel et al. 1987). There was a linear decrease in clearance with increasing age (1.3–30.0 years) regardless of the sex (Gardner and Jusko 1982).

In healthy volunteers and patients with asthma, 20–87-years old and receiving theophylline, although clearance did not fall with increasing age during younger adult life, there was a fall during late adult life, becoming apparent in the seventh, eighth, and ninth decades of age with a reduction in the basal rate of theophylline metabolism (Crowley et al. 1988; Jackson et al. 1989) and plasma clearance of theophylline was 30% lower in elderly male subjects than in young male subjects (Loi et al. 1997). A considerably higher interindividual variability in the disposition of theophylline was observed in frail elderly women (Groen et al. 1993).

Gender and hormones. There were statistically significant differences ($P < 0.01$) in the theophylline kinetic parameters, such as the elimination half-life, 8.70 ± 0.60 h

during proestrus, 4.61 ± 0.16 h during estrus, and 5.01 ± 0.85 h during diestrus, and the AUC were 214.61 ± 3.58, 128.64 ± 9.64, and 165.57 ± 23.86 μg h/mL, respectively (Bruguerolle 1987). In pregnant rats, theophylline was eliminated at a slower rate than in both lactating rats and virgin controls, resulting in a longer half-life and lower clearance, while the volumes of distribution in pregnant, lactating, and control rats were not different (Brandstetter et al. 1986) and the impaired theophylline metabolism in late pregnancy exhibited increased excretion of unchanged theophylline with decreased formation (−68%) of 1,3DMU and (−30%) of 1MU (Arnaud et al. 1982a, b).

The elimination of theophylline does not differ between men and women (Jusko et al. 1979; Powell et al. 1977). Several other studies looking at the effect of gender on theophylline clearance in children (8 years) reported that gender had no effect on theophylline clearance (Ellis et al. 1976; Yano et al. 1993), but male children aged 4–20 years were shown to have significantly higher theophylline clearances (31 and 22%, respectively) than female children in other studies (Gardner and Jusko 1982; Driscoll et al. 1989; Igarashi and Iwakawa 2009). In healthy men and premenopausal women, statistically significant gender-related effects were seen for the theophylline half-life and clearance (Jennings et al. 1993). The disposition of theophylline throughout pregnancy and in the postpartum period showed that theophylline clearance was slightly affected during the first two trimesters (2.61–2.85 L/h), while a statistically significant reduction was observed late in pregnancy (2.05 L/h). The postpartum clearance values suggest an ongoing suppression relative to prepregnancy levels. A significant higher half-life of 13.00 ± 2.31 h was observed during the third trimester when compared to 9.53 ± 3.53 h in the postpartum period. The absolute volume of distribution increased with gestation (Gardner et al. 1987). Chronic oral contraceptive users exhibited significantly lower total plasma theophylline clearance (−30%) and the half-life was also significantly prolonged from 7.3 to 9.8 h, while the volume of distribution was unchanged (Tornatore et al. 1982; Teichmann 1990). In contrast, acute oral contraceptive exposure failed to induce significant changes (Gardner et al. 1983).

Physical exercise. The volumes of theophylline distribution decreased significantly after exercise in the heat, apparently due to dehydration (Schlaeffer et al. 1984; Lenz et al. 2004).

Obesity. Age was the most important determinant of theophylline clearance in pediatric patients and weight had less effect than age and did not statistically improve the model ($P > 0.005$) when combined with age (Driscoll et al. 1989). In obese and normal subjects, the apparent volume of distribution measured from the total body weight (TBW) or the ideal body weight (IBW) averaged 0.482 L/kg TBW in normal subjects and 0.382 L/kg TBW in obese subjects and 0.77 L/kg IBW in obese subjects. Clearance averaged 63.0 mL/h/kg IBW in normal subjects and 32.8 mL/h/kg TBW and 64.1 mL/h/kg IBW in obese subjects. The mean half-lives were longer in obese subjects than in normal subjects, 8.6 ± 2.0 and 6.0 ± 2.1 h, respectively (Gal et al. 1978).

Drugs. As expected from the metabolism described already, theophylline pharmacokinetics can be influenced by drugs, herbal supplements, and diet. The extensive

literature on the interactions of drugs with theophylline will not described here. A review on the interaction of drugs has been published describing an increase or a decrease of theophylline clearance (Upton 1991). One aspect that needs mentioning is that theophylline is demethylated to 1MX and 1MU was produced from a rapid xanthine oxidase mediated 8-oxidation, while no 1MU was formed by 3-demethylation of 1,3DMU (Birkett et al. 1983).

Cigarette smoking appeared to induce theophylline metabolism as reflected by the mean theophylline half-life in smokers (5.4 h) versus nonsmokers (8.3 h) (Jusko 1979; Jusko et al. 1979; Powell et al. 1977). Cigarette smoking significantly altered the theophylline clearance processes (Schrenk 1998; Teichmann 1990; Jennings et al. 1993; Zevin and Benowitz 1999) and a 40% elevation in theophylline clearance was observed in women who smoked (Gardner et al. 1983).

Daily caffeine intake significantly altered the theophylline clearance processes (Gardner et al. 1983). On caffeine administration, the theophylline steady-state concentration and AUC increased by 23 and 40%, respectively, and the reduction in the apparent total body clearance and elimination rate constant of theophylline reached 29 and 31%, respectively, indicating a pronounced influence on theophylline of concomitant ingestion of caffeine in normal consumers (Jonkman et al. 1991). Abstention from methylxanthine-containing foods and beverages led to a significant decrease in the elimination half-life ($P < 0.02$) owing to increases in the elimination constants for theophylline, 3MX, and 1,3DMU (Monks et al. 1979). However, in contrast to the effect of deprivation of dietary methylxanthines, the addition of extra methylxanthines from six bottles per day of a cola beverage to the diet did not influence the disposition of theophylline (Monks et al. 1981).

Diseases. As well as for caffeine, diseases that compromise liver function, especially cirrhosis, reduce theophylline clearance in animals and man (Park et al. 1999; Nam et al. 1997; Amodio et al. 1991). There is also a small effect in diabetes mellitus rats induced by alloxan or streptozotocin (Kim et al. 2005). In patients with insulin-dependent diabetes mellitus and in sex-, age-, and weight-matched healthy nonsmokers, the pharmacokinetic parameters of theophylline, plasma clearance, elimination half-life, and volume of distribution were similar, but there was a positive correlation between hemoglobin A1c values and plasma theophylline clearance ($P < 0.05$), formation clearance of 1,3DMU ($P < 0.05$), and formation clearance of 1MU ($P < 0.05$) (Korrapati et al. 1995). Among animal and human studies, renal disease, Down syndrome, psoriasis, endotoxin-induced fever, acidosis, hypoxia, hyperlipidemia, and hypoalbuminemia were shown to alter the pharmacokinetics of theophylline.

3.7 Metabolites and Metabolic Pathway

The methylation of theophylline to caffeine was shown in rat (Gorodischer et al. 1986b) and in rat fetus (Arnaud et al. 1982a, b), in premature infants (Boutroy et al. 1979; Bory et al. 1979), and in vitro in the human fetal liver (Aranda et al. 1979).

In premature infants, plasma concentrations of caffeine increased from 1.8 mg/L at day 1 to 3.7 mg/L 7 days after initiation of theophylline therapy. Labeled caffeine, paraxanthine, and theobromine were found in plasma and urine of preterm newborns receiving [1,3-^{15}N],[2-^{13}C]theophylline for the treatment of primitive apneas, showing that theophylline was converted to caffeine by N7-methylation (Brazier et al. 1980b). Several studies confirmed this methylation pathway in the newborn (Soyka et al. 1981; Simons et al. 1981). This pathway was believed to be specific to the neonatal period, explained by the immaturity of liver enzymes. However, caffeine (0.21–0.75 mg/L) and its major metabolite, paraxanthine, were observed in plasma following oral administration of theophylline (8.1–21.5 mg/L) in a multiple-dose study in healthy subjects. In adult subjects, about 6% of the theophylline dose was converted to caffeine (Tang-Liu and Riegelman 1981; Arnaud 1984). Only 7–19% of theophylline is excreted unchanged in the urine with other metabolites, including 1,3DMU (35–55%), 1MU (13–26%), 3MX (9–18%), 1MX (0.3–4%), and 3MU (1%) (Arnaud 1984; Birkett et al. 1985; Anonymous 1991). The N3-demethylation of theophylline accounted for 34 ± 6% of the urinary metabolites, N1-demethylation of theophylline for 15 ± 3%, and C8-oxidation of theophylline for 51 ± 9%. The C8-oxidation of 1MX and 3MX corresponded to 93 ± 4 and 9 ± 4%, respectively, of the excreted monomethylxanthine and urate. In addition to theophylline, 1,3DMU and 1MU were consistently found in plasma and saliva. Theophylline accounted for 91 ± 4% of the total plasma AUC, with 1,3DMU accounting for 3.1 ± 1.4%, 3MX for 3.4 ± 1.8%, and 1MU for 2.5 ± 1.5% (Rodopoulos and Norman 1997). Urinary excretions of 1,3DMU and 1MU exhibited the highest correlations, while the poorest correlations were observed for 1MX compared with those of 1MU and 1,3DMU, suggesting that 1MU did not derive solely from 1MX and implicating 1,3DMU as an alternative precursor (Bayar and Ozer 1997). However, previous results on oral administration of 1,3DMU in healthy male volunteers showed that 1,3DMU was recovered unchanged in urine and was not demethylated to 1MU (Birkett et al. 1983). The quantitative urinary excretion of theophylline metabolites in man and in various animal species, expressed as the percentage of the administered dose, is shown in Table 1.

4 Theobromine

When compared with caffeine and theophylline, fewer studies have been performed on theobromine.

4.1 Absorption

In rats there is complete absorption of theobromine, with only 1% of the dose excreted in feces as unchanged theobromine (Arnaud and Welsch 1979a; Bonati et al. 1984) and 94–106% was recovered in urine (Shively and Tarka 1983).

A marked decrease of the absorption rate constant was observed with increased dose, but the absolute bioavailability of theobromine remained 100%. As a consequence, the peak blood level tends to appear later with larger doses (Bonati et al. 1984). Theobromine bioavailability after an oral administration in healthy, nonmedicated, nonsmoking men and after 14 days' abstention from all methylxanthine sources was 0.96 ± 0.02 (Tarka et al. 1983; Miners et al. 1982; Yesair et al. 1984). Both the rate and the extent of absorption of theobromine in chocolate were less than those of theobromine in solution and the relative bioavailability of theobromine in chocolate was 80%, suggesting food interaction with chocolate ingredients (Shively et al. 1985). Theobromine absorption after oral administration of capsules and chocolate candy was compared in volunteers who abstained from methylxanthines. A theobromine plasma C_{max} of 6.72 μg/mL was measured 3 h after ingestion of a capsule containing 370 mg theobromine and absorption of the same dose from chocolate was more rapid and produced a higher C_{max} of 8.05 μg/mL after 2 h (Mumford et al. 1996).

4.2 Distribution

One day after the oral administration of [7-Me-^{14}C]theobromine to rats, no organ accumulation of theobromine and metabolites could be seen by whole-animal autoradiography and the most labeled organ was the liver, with 0.4% of the administered radioactivity and 2% was present in the cecum and the colon coming from intestinal and bile secretion (Arnaud and Welsch 1979a). Theobromine was shown to cross the placenta in the pregnant rat (Arnaud and Gétaz 1983).

In rats, blood samples taken at various intervals, from 0.5 to 3 h, showed that the mean value of the unbound theobromine fraction was 0.88 (Bonati et al. 1984). In plasma of pregnant and nonpregnant rats, theobromine corresponds to about 99% and metabolites to less than 1% (Shively and Tarka 1983).

When [8-^{14}C]theobromine was administered to newborn rats and on the following days, it was shown that the brain/blood theobromine concentrations ratio decreased continuously from 0.96 ± 0.02 at birth to 0.60 ± 0.02 in 30-day-old rats, while the liver/blood ratio remained constant at 1.18 ± 0.05. These results have been interpreted as a postnatal blood–brain barrier for theobromine in the rat (Arnaud and Gétaz 1982). The theobromine concentration was shown to be in equilibrium between blood, brain, and liver of the fetus and blood of the pregnant rat (Arnaud and Gétaz 1983). In man, theobromine is distributed throughout the total body water (Yesair et al. 1984). Milk chocolate containing theobromine (240 mg) was ingested by nursing mothers and peak theobromine concentrations of 3.7–8.2 mg/L were found in all fluids, including plasma, saliva, and breast milk, at 2–3 h after ingestion (Resman et al. 1977). In in vitro and in vivo studies, the fraction of theobromine unbound to plasma proteins averaged 0.90 over a wide range of concentrations (Bonati et al. 1984).

Compared with the fetus, the AUC values of theobromine were lower in the brains of adults compared with plasma, confirming that theobromine might be selectively excluded from the adult brain (Wilkinson and Pollard 1993). Theobromine and caffeine milk-to-serum concentration ratios were twofold higher compared with those of paraxanthine and theophylline (McNamara et al. 1992). The mean concentration ratio of theobromine in nursing mothers was 0.82 ± 0.17 for milk/plasma and if a mother ate a 4-oz chocolate bar every 6 h and the infant nursed when the theobromine concentration in milk was at its peak, the infant could ingest about 10 mg of theobromine per day (Resman et al. 1977).

The theobromine concentrations in plasma and saliva were similar, after a 500-mg oral dose, whereas the saliva concentrations for 7MX and 3MX were found to be 63 ± 17% of the plasma concentrations for 7MX and 74 ± 13% for 3MX, respectively (Rodopoulos et al. 1996).

4.3 Excretion

In rats, urine excretion was the main excretory route and amounted to 84 ± 8% of the administered dose (Arnaud and Welsch 1979a; Bonati et al. 1984). Urinary excretion was compared in rats, mice, hamsters, and male rabbits and dogs after oral administration of [8-^{14}C]theobromine and about 60–89% of the dose was recovered in urine (Miller et al. 1984).

Theobromine was shown to be extensively reabsorbed in the renal tubule and its renal clearance was highly urine flow dependent and thus urinary excretion varied with urine output (Tang-Liu et al. 1983). After the ingestion of 1 g theobromine, 62% of the dose was recovered in 48-h urine collected in adult subjects and unchanged theobromine, 3MX, 7MX, and 7MU were identified (Cornish and Christman 1957). After a single oral dose of theobromine with a trace amount of [8-^{14}C]theobromine had been administered to healthy nonsmoking men, 50% of the radioactivity was recovered in urine after 8–12 h and the entire radioactivity administered was found after 3 days (Tarka et al. 1983). The cumulative urinary excretion of radioactivity from [8-^{14}C]theobromine in subjects who maintained 14 days of methylxanthine abstention was 86.4% (80–96%) and in the same subjects not limited in their methylxanthine consumption the excretion in urine amounted to 81.1% (81–93%) (Shively et al. 1985).

After the administration of [7-Me-^{14}C]theobromine (1–6 mg/kg) to male rats, fecal excretion amounted to 11 ± 1% of the administered dose, but only 10% was unchanged theobromine and incubation of theobromine into the gastrointestinal content showed no metabolic transformation, suggesting that the metabolites found were excreted through gastrointestinal secretion (Arnaud and Welsch 1979a). After oral administration of [8-^{14}C]theobromine to rats, similar amounts of radioactivity (2.5%) were recovered in feces as after intravenous administration (Bonati et al. 1984). In pregnant rats, the oral administration of [8-^{14}C]theobromine showed that fecal excretion amounted to 31% of the ingested dose (Arnaud and Gétaz 1983).

Fecal excretion was compared in rats, mice, hamsters, and male rabbits and dogs after oral administration of [8-^{14}C]theobromine and from 2 to 38% of the dose was recovered in feces. In male and female rats, 38.2 ± 0.8 and 16.2 ± 1.3% were excreted in feces, respectively, and the values were 8.8 ± 1.1 and 11.5 ± 1.8% for mice, 15.0 ± 6.0% and 14.3 ± 3.3% for hamsters, and 1.6 ± 0.2% male rabbits and 4.5 ± 0.1% for male dogs (Miller et al. 1984). However, bentonite was often added to the rodent diet as a pellet binder and may explain the higher fecal excretion reported in rats (Arnaud 1983). Fecal elimination of [8-^{14}C]theobromine-derived radioactivity after the oral administration of a tracer dose in subjects who maintained or did not maintain 14 days of methylxanthine abstention was 0.56–0.54 and 0.15–1.42%, respectively (Shively et al. 1985).

4.4 Pharmacokinetics

The half-life of theobromine in rats exhibited large variations from 1.9 to 6.4 h, with an average value similar to that reported for man of 6.1 ± 0.7 h (Drouillard et al. 1978). The kinetics of theobromine in rats after a dose ranging from 1 to 100 mg/kg and chronic intake showed no significant difference in the pharmacokinetic profile except for a reduction in the absorption rate constant as the dose increased. Linear pharmacokinetics was observed up to the dose of 100 mg/kg and the AUC values increased in proportion to the dose (Bonati et al. 1984). Pregnancy in rats on day 19 of gestation did not affect the pharmacokinetics of theobromine (15–100 mg/kg orally) and similar values were obtained in nonpregnant rats. No dose-dependent kinetics was observed in the theobromine plasma half-life, volume of distribution, systemic clearance, dose-normalized AUC, or T_{max} (Shively and Tarka 1984). A decrease in the elimination rate constant of theobromine was observed at the highest dose of 50 mg/kg (1–100 mg/kg/day) in rabbits, suggesting saturation (Latini et al. 1984).

The half-life of theobromine in nursing mothers after ingestion of milk chocolate containing 240 mg of theobromine averaged 7.1 ± 2.1 h, body clearance was 65 ± 20 mL/h/kg, and the apparent volume of distribution was 0.62 ± 0.13 L/kg (Resman et al. 1977). A similar mean value of the half-life was reported 1 year later from measurements in man and was 6.1 ± 0.7 h (Drouillard et al. 1978). Theobromine disposition follows first-order kinetics with a one-compartment open model and the mean theobromine half-life was 9.28 ± 0.7 h, plasma clearance was 0.87 ± 0.06 mL//min/kg, the AUC was 117 ± 7.9 mg h/L, and the volume of distribution was 0.68 ± 0.03 L/kg (Tarka et al. 1983). In healthy volunteers the total plasma clearance and renal clearance for theobromine were 46 and 67% greater than those for theophylline, respectively, but most of the difference was due to the lower protein binding of theobromine with the free fraction of 0.86 compared with 0.58 for theophylline. Clearance by 3-methyl demethylation was 3.7-fold higher for theobromine than for theophylline. There were high degrees of correlation between theophylline and theobromine plasma clearances, partial metabolic clearances, and renal clearances (Birkett et al. 1985; Lelo et al. 1986a). Correlation between renal

clearance of theobromine and the urine flow rate was reported (Trang et al. 1985). A supplement of theobromine (6 mg/kg) given to healthy men did not modify significantly theobromine pharmacokinetics and a similar half-life, apparent volume of distribution, and clearance were reported (Shively et al. 1985).

4.5 Metabolism

In human liver microsomes, at least two distinct liver enzymes, isozymes of CYP, with differing substrate affinities have the potential to catalyze theobromine N-demethylations and C8-hydroxylations. At the low theobromine concentrations encountered in vivo, the high-affinity site is expected to predominate (Campbell et al. 1987a). The identification of the CYP isoforms responsible for the conversion of theobromine to its primary metabolites was studied in human liver microsomes using various specific inhibitors. Furafylline variably inhibited 7MX formation from theobromine, but had no effect on other pathways. Diethyldithiocarbamate and 4-nitrophenol, probes for CYP2E1, inhibited the formation of 3MX, 7MX, and 3,7-dimethyluric acid (3,7DMU) by approximately 55–60, 35–55, and 85%, respectively. Recombinant CYP1A2 and CYP2E1 enzymes exhibited similar values of the apparent Michaelis–Menten constant (K_m) for 7MX formation, and CYP2E1 was further shown to have the capacity to convert theobromine to both 3MX and 3,7DMU (Gates and Miners 1999). The total plasma and partial metabolic and renal clearances of theobromine determined in healthy volunteers supported the view that theobromine was metabolized by a common group of CYPs under similar regulatory control and it was proposed to use theobromine to assess the activity of these enzymes in man (Birkett et al. 1985). It was suggested that 3,7DAU and 3,7DMU are derived from a common oxidized intermediate of theobromine which is the precursor of 3,7DMU, but in the presence of glutathione (GSH) or some other cellular thiol it may be reduced to give 3,7DAU (Lelo et al. 1990). The involvement of GSH and CYPs in the conversion of theobromine to 3,7DAU and 3,7DMU has been demonstrated in rat liver microsomes, showing that the ratio of formation of 3,7DAU to 3,7DMU increased with increasing GSH concentration to a maximum of 12:1 for 2 mM. When compared with untreated animals, 3,7DAU and 3,7DMU formation was increased approximately 12- and 1.6-fold in liver microsomes of rats treated with 3-methylcholanthrene and phenobarbitone, respectively (Lelo et al. 1990).

4.6 Sources of Variation in Theobromine Pharmacokinetics and Metabolism

Gender and hormones. The kinetic parameters of pregnant and nonpregnant rats were similar at all theobromine dose levels studied (Shively and Tarka 1983). In rabbits there was also no significant difference due to either gender or pregnancy

(Latini et al. 1984). The most important theobromine metabolite excreted by mice was 3,7DAU and male mice converted theobromine to this metabolite more extensively than did female mice. There was significantly more 3,7DMU in female rats than in male rats (Miller et al. 1984).

Drugs. Allopurinol had no effect on the clearance of theobromine, suggesting that the elimination of theobromine is not dependent on xanthine oxidase (Miners et al. 1982).

Smoking. As expected, theobromine plasma clearance was 33% higher in smokers than in nonsmokers owing to induction of all metabolic pathways, but 7-demethylation was induced to a greater extent than the other pathways (Miners et al. 1985; Gates and Miners 1999).

Diet. The mean theobromine half-life, apparent volume of distribution, and clearance were unaffected by abstinence from all methylxanthines or receiving high daily doses of theobromine from chocolate for 1 week (Shively et al. 1985). However, a previous study (Drouillard et al. 1978) suggested that immediately after five daily doses of theobromine, an impairment of theobromine clearance occurred that was reversible by 4 days of dietary abstention from methylxanthines.

4.7 Metabolites and Metabolic Pathway

After the administration of [7-Me-^{14}C]theobromine (1–6 mg/kg) to male rats, the radioactivity collected in $^{14}CO_2$ corresponding to the formation of 1-methyl and 3-methyl derivatives amounted to 6 ± 1% of the administered dose. In urine unchanged theobromine (49 ± 4% of excreted metabolites), 3,7DAU (36 ± 4%), 7MX (6 ± 1%), 7MU (3.9 ± 0.5%), 3,7DMU (2.7 ± 0.2%) and trace amounts of *N*-methylurea and dimethylallantoin were found (Arnaud and Welsch 1979a). Urinary excretion of unchanged theobromine increased in the pregnant rat from 47 ± 4 to 74 ± 3%, while urinary excretion of 3,7DAU decreased from 35 ± 4% to 22 ± 2%, thus showing that pregnancy impaired theobromine metabolism (Arnaud and Gétaz 1983; Bonati et al. 1984). After an oral dose of 5 and 100 mg/kg theobromine, pregnant and nonpregnant rats showed similar qualitative metabolic patterns and the metabolites identified in the urine were theobromine (39–62%), 37DAU (20–32%), 3MX and 7MX (8–15%), 3,7DMU (5–10%), and 7MU (5–7%) (Shively and Tarka 1983). Unchanged theobromine corresponded to about 50% of urinary metabolites in rat and dog, 32.4 ± 2.2% of the administered dose in rat and 36.8 ± 5.9% in dog, about 30% of urinary metabolites for mouse and hamster, 22.1 ± 3.6% of the dose in mouse and 20.0 ± 2.8% in hamster, and less than 20% of urinary metabolites for rabbit, 13.9 ± 2.7% of the dose (Latini et al. 1984). 3,7DAU was the most important metabolite after theobromine and corresponded to 25% of urinary metabolites in rat (16.5 ± 0.9% of the dose), mouse (13.9 ± 2.1% of the dose) and hamster (14.6 ± 1.6% of the dose), while it represented only 10% of urinary metabolite in rabbit (10.0 ± 1.1% of the dose)

and dog (7.5 ± 3.1% of the dose). In rabbit, 7MX (35.5 ± 3.2% of the administered dose) and 3MX (8.4 ± 0.5% of the dose) corresponded to about 50 and 11% of urine metabolites while 3,7DMU (1.5 ± 0.1%), 7MU (1.6 ± 0.2%), and 3MU (0.6 ± 0.1%) were minor metabolites. In hamster, 7MX (11.4 ± 1.0% of the administered dose) corresponded to 20% of urine metabolites and 3MX (2.3 ± 0.2%), 7MU (2.9 ± 0.4%), 3MU (0.3 ± 0.1%), and 3,7DMU (2.3 ± 0.6%) were minor metabolites. In dog, 3MX (19.9 ± 2.7% of the administered dose) corresponded to 25% of urine metabolites and 7MX (3.4 ± 0.9%), 7MU (4.4 ± 2.2%) ,and 3,7DMU (0.4 ± 0.1%) were less important. In mouse, 7MX (8.2 ± 0.4% of the administered dose) and 7MU (5.3 ± 0.2% of the dose) both corresponded to less than 10% of urine metabolites and 3MX (3.2 ± 0.2%), 3MU (0.4 ± 0.1%), and 3,7DMU (2.5 ± 0.3%) were minor metabolites. In rat, 3MX (3.9 ± 0.3% of the administered dose), 3,7DMU (2.1 ± 0.2% of the dose), and 7MX (2.5 ± 0.1% of the dose) corresponded to about 5% of urine metabolites and 7MU (1.3 ± 0.1%) was less important and 3MU could not be quantified. Demethylation of theobromine was greatest in rabbits and lowest in rats and 3-methyl demethylation predominated over 7-methyl demethylation in all species except the rat and the dog. In dog, demethylation of theobromine was most important on 7-methyl, while in rat there was no specific demethylation activity. Oxidation to uric acids was a minor metabolic pathway in all species, with the greatest activity in mice. In addition to these identified metabolites, an unidentified but apparently unique metabolite was detected in dog (Miller et al. 1984).

In healthy, nonmedicated, nonsmoking men after 14 days' abstention from all methylxanthine sources, the urine metabolites measured were theobromine (18.2 ± 2.1%), 7MX (33.6 ± 1.6%), 7MU (7 ± 0.7 %), 3MX (19.9 ± 0.9%), 3,7DAU (5.7 ± 0.9%), and 3,7DMU (1.0 ± 0.2%) (Tarka et al. 1983). After the oral administration of a dose of [8-^{14}C]theobromine, the percentage of urinary metabolites recovered consisted of 42% 7MX, 20% 3MX, 18% theobromine, 10% 7MU, and 10% 3,7DAU (Shively et al. 1985). In urine collected 48 h after administration of a 500-mg theobromine dose, unchanged theobromine accounted for 21 ± 4% of total urine excretion and 36 ± 5% for 7MX, 21 ± 4% for 3MX, 11 ± 4% for 3,7DAU, 10 ± 2% for 7MU, 1.3 ± 0.6% for 3,7DMU and 0.5 ± 0.4% for 3MU. The N3-demethylation of theobromine accounted for 58 ± 7% of the urinary metabolites, the N7-demethylation of theobromine for 27 ± 6%, the C8-oxidation of 7MX for 22 ± 4%, the C8-oxidation of 3MX for 2 ± 2%, and the formation of 3,7DAU for 13 ± 4% (Rodopoulos et al. 1996). The quantitative urinary excretion of theobromine metabolites in man and in various animal species, expressed as the percentage of the administered dose, is shown in Table 1.

5 Paraxanthine

Plant biosynthesis leads to the accumulation of caffeine, theobromine, and theophylline, while only trace amounts of paraxanthine were identified as a constituent of *Coffea arabica* (Arnaud and Enslen 1992). The absence of food containing

paraxanthine has limited the number of studies investigating its metabolic fate. As 80% of caffeine ingested by humans is transformed through paraxanthine and the average serum levels of paraxanthine are two thirds those of caffeine, the contribution of paraxanthine to the pharmacological activity of caffeine needs to be considered in understanding the clinical pharmacological activity of caffeine, particularly with chronic, repetitive caffeine consumption (Benowitz et al. 1995).

5.1 Absorption and Distribution

It is believed that paraxanthine absorption from the gastrointestinal tract, like the other methylxanthines, was complete after an oral dose (Lelo et al. 1989).

The concentration of radioactivity in the blood and the liver 2 h after oral administration was the same, indicating a complete equilibrium between blood and the tissues except for the brain (Arnaud and Enslen 1992). Twenty-four hours after intravenous administration of [1-Me-^{14}C]paraxanthine to rats, there was no accumulation in the body as seen by whole-animal-body autoradiography and the cumulated dose measured in organs reached 0.2% of the dose (Arnaud and Welsch 1979b). Whole-animal-body autoradiography showed a wide distribution throughout the body in liver, heart, muscle, thymus, lungs, and the gastrointestinal tract 0.5 h after [8-^{14}C]paraxanthine had been given orally to rats. Higher concentrations were observed in the stomach, the kidney, and the bladder, showing that a fraction of the dose had still not emptied from the stomach and that another fraction had already been excreted in the urine. After 10 h, only traces of radioactivity were detected in the body (Arnaud and Enslen 1992).

Brain. The radioactivity from [8-^{14}C]paraxanthine 2 h after oral administration was lower in the brain, which is protected by a blood–brain barrier, and the brain-to-blood concentrations ratio was 0.30 for paraxanthine, while this ratio is 1 for caffeine (Arnaud and Enslen 1992). Subcutaneous injection of caffeine into rats resulted in higher concentrations of methylxanthines, particularly paraxanthine, in the striatum than in the rest of the brain and it was observed that the clearance of paraxanthine was faster in serum than in brain structures (Parra et al. 1991). However, an alternative explanation is that paraxanthine binding to abundant A_{2A} receptors in the striatum delayed elimination. Compared with the fetus, the AUC value of paraxanthine was found to be lower in the brains of adults compared with plasma after a dose of 25 mg/kg. This suggests that paraxanthine might be partly excluded from the adult brain (Wilkinson and Pollard 1993).

The distribution into milk of paraxanthine measured in lactating New Zealand white rabbits following a bolus dose of caffeine showed that the milk-to-serum paraxanthine concentration ratio was 0.358 ± 0.019. Paraxanthine and theophylline have the lowest ratios, about half those of caffeine and theobromine (McNamara et al. 1992).

5.2 Excretion

A systematic survey of individual pollutants in a sewage treatment plant receiving urban wastewater recently showed that paraxanthine was one of the main product found in concentrations over 20 ppb (Rosal et al. 2010). Paraxanthine has been identified in human urine (Salomon 1883) and then recovered unchanged in wastewater. The most frequently detected compounds in surface water on the coastline within the western Lake Erie basin were caffeine (88%) and paraxanthine (56%), which was detected with a maximum concentration of 1.8 μg/L (Wu et al. 2009). Intravenous administration of [1-Me-^{14}C]paraxanthine to rats showed that 1 day after injection 7 ± 1% was recovered in feces (Arnaud and Welsch 1979b).

Intravenous administration of [1-Me-^{14}C]paraxanthine to rats showed that the main excretory pathway was urine ,where 85 ± 3% of the administered dose was recovered (Arnaud and Welsch 1979b). In man, approximately 60% of orally administered paraxanthine may be recovered as unchanged in the urine (Arnaud and Welsch 1980a) and after caffeine administration to healthy subjects, paraxanthine was excreted in the urine in amounts sixfold higher than caffeine (Arnaud and Welsch 1980a; Callahan et al. 1982). Paraxanthine was extensively reabsorbed in the renal tubule and its renal clearance was highly urine flow dependent and thus urinary excretion varied with urine output (Tang-Liu et al. 1983).

5.3 Pharmacokinetics

The pharmacokinetics of paraxanthine given intravenously in different doses to rats showed that the fraction bound was 15% and remained constant in the plasma for a concentration range of 1–100 μg/mL. Paraxanthine elimination followed first-order kinetics for a dose up to 10 mg/kg and the blood concentrations versus time data were described by a one-compartment, open model system. The mean half-life and elimination rate constant were 1 h and 0.70/h, respectively. The average apparent volume of distribution was 1.50 L/kg and the total clearance was 0.90 L/h/kg. After larger doses (15 and 30 mg/kg), the kinetics were nonlinear and the AUC increased, but not in proportion to the dose. These findings indicated that paraxanthine in the rat is eliminated by a saturable process with an apparent K_m of about 31 μg/mL and an apparent maximum rate of metabolism of about 0.40 μg/mL/min (Bortolotti et al. 1985; Arnaud and Enslen 1992). In rabbit, paraxanthine clearance was not dose-dependent (Dorrbecker et al. 1987).

The elimination of paraxanthine after its formation has been shown not to follow linear kinetics (Tang-Liu et al. 1983). A relationship has been established between renal clearance of paraxanthine and the urine flow rate (Trang et al. 1985). The partial clearance of caffeine to paraxanthine was eightfold and 23-fold greater than that of theobromine and theophylline, respectively (Lelo et al. 1986b). The

clearances of paraxanthine and caffeine were similar, 2.20 and 2.07 mL/min/kg, respectively and were twofold lower for theophylline and theobromine (Lelo et al. 1986a). After a single dose of 3–4 mg/kg paraxanthine, a mean half-life of 3.9 ± 0.7 h was reported (Lelo et al. 1986a, 1989). The volume of distribution at the steady state of paraxanthine was similar to that of caffeine and theobromine (0.63–0.72 L/kg) and was higher than that of theophylline (0.44 L/kg) (Lelo et al. 1986a).

The administration of [8-^{14}C]caffeine (40 mg/kg) to various mouse strains showed higher plasma paraxanthine concentrations in the CBA/J strain compared with the SJL/J, A/J, and SWR/J strains. This effect may be explained by differences in the capacity for paraxanthine glucuronidation. The ratio of the plasma concentration of paraxanthine to total methylxanthine was 7–12% after 0.5 h and increased after 8 h to 29% for the SJL/J and A/J strains andto 44–52% for the CBA/J and SWR/J strains. Paraxanthine was the most important methylxanthine 4 h after caffeine administration for the CBA/J and SWR/J strains but not for the SJL/J and A/J strains, where similar concentrations of paraxanthine and caffeine are observed (Arnaud et al. 1989). There were no differences in the blood pharmacokinetics of paraxanthine between CYP1A2-null and wild-type mice (Labedzki et al. 2002).

Allopurinol pretreatment had no effect on paraxanthine plasma clearance but decreased 1MU excretion and increased 1MX excretion, with the combined excretion of these metabolites remaining constant (Lelo et al. 1989). Among the high degree of interliver variation in metabolic rates, smokers showed the second highest activity among a 20-fold range in paraxanthine demethylation rates (Campbell et al. 1987a).

5.4 Metabolism

The main metabolite of paraxanthine was 1MX both in human and in wild-type mice liver microsomes. In contrast, in CYP1A2-null murine liver microsomes, the main paraxanthine metabolite was 7MX (Labedzki et al. 2002). It was suggested that the formation of paraxanthine may be a better indicator of in vivo CYP1A2 activity than caffeine levels (Bapiro et al. 2005). The high value of the CYP1A2 index defined as urinary AFMU plus 1MX plus 1MU to 1,7DMU could be explained by a low urinary concentration of 1,7DMU and was suggested to be affected by the whole deleted allele of CYP2A6 (CYP2A6*4) in healthy Japanese volunteers. It was shown that CYP2A6 and CYP1A2 exhibited high catalytic activities for the paraxanthine 8-hydroxylation, which was significantly associated with coumarin 7-hydroxylase activities ($P < 0.01$) in liver microsomes. Tranylcypromine, an inhibitor of CYP2A6, reduced the paraxanthine 8-hydroxylase activities of human liver microsomes. Paraxanthine 8-hydroxylase activities were also found to be low in liver microsomes from individuals possessing deletion of or mutations in the CYP2A6 gene, suggesting that CYP2A6 is a main paraxanthine

8-hydroxylase and this activity is reduced by the genetic polymorphisms of the CYP2A6 gene (Kimura et al. 2005). Children had a higher urine metabolite ratio of paraxanthine 7-demethylation to 8-hydroxylation ($P < 0.001$) than adults (Campbell et al. 1987b).

5.5 *Metabolites and Metabolic Pathways*

Paraxanthine is the main pathway (75–80%) of the first step of caffeine metabolism in man (Arnaud and Welsch 1980a), while it represents a maximum of 40% in rats, 65% in mice, 55% in Chinese hamsters, and less than 10% in monkeys. Rabbits seems the closest model to man, but with a relative inefficiency for further metabolizing paraxanthine (Dorrbecker et al. 1987). The mean fractional conversion of caffeine to paraxanthine was 79.6 ± 21%, while it was only 10.8 ± 2.4% for theobromine and 3.7 ± 1.3% for theophylline. Demethylation pathways accounted for 83.9 ± 5.4% for paraxanthine and only 12.1 ± 4.1% for theobromine and 4.0 ± 1.4% for theophylline (Lelo et al. 1986b). The combined formation of the 7-demethylated products (1MX, 1MU) and AFMU was found to account for 67% of paraxanthine clearance. Formation of 7MX and 1,7DMU and renal excretion of unchanged paraxanthine corresponded to 6, 8, and 9% of paraxanthine clearance, respectively. Data from the effect of allopurinol and cimetidine are consistent with 1MX and AFMU being derived from a common intermediate (Lelo et al. 1989).

Unchanged paraxanthine was the most important urine metabolite in rats, 52 ± 3%, and 1,7DMU with the uracil derivative 1,7DAU both corresponded to 15 ± 2% of the dose excreted. Paraxanthine 1-methyl demethylation with the formation of 7MX and 7MU is a minor pathway (2.3 ± 0.2%), while 7-methyl demethylation was the most important with urine excretion of 1MX (11 ± 1%) and 1MU (21 ± 3%) (Arnaud and Welsch 1979b). Important species differences were shown for paraxanthine metabolism (Arnaud 1985) and a glucuroconjugate of paraxanthine was identified only in mice (Arnaud et al. 1986b). Paraxanthine and paraxanthine glucuronide urine excretion in mice showed an inverse relationship in CBA/J (17 ± 5 and 9.5 ± 3%, respectively), SJL/J (10.5 ± 3.5 and 21.0 ± 2%), A/J (7 ± 1 and 25 ± 1.5%) and SWR/J (14.5 ± 4 and 19 ± 6%) strains (Arnaud et al. 1989).

The analysis of the metabolites in urine collected at 24-h showed with unchanged paraxanthine (10 ± 4% of the administered dose) the presence of 1MX (15 ± 4%), 1MU (17 ± 2%), 1,7DMU (15 ± 3%), 1,7DAU (4 ± 2%), 7MX (5 ± 3%), AFMU (18 ± 6%), and 7MU (4 ± 3%) (Arnaud and Welsch 1980a; Callahan et al. 1982). The quantitative urinary excretion of paraxanthine metabolites in man and in various aniumal species, expressed as the percentage of the administered dose, is shown in Table 1.

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